Treatment of Chronic Tinnitus with Neurofeedback

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Abstract

Chronic tinnitus is an auditory phantom percept emerging from unsuccessful compensatory mechanisms in the brain as a result of damage to inner ear receptor cells. Unfortunately, an effective treatment to completely alleviate tinnitus symptoms has not yet been discovered. Newer developments, however, suggest that neurofeedback, which aims at altering typical neural activity patterns related to tinnitus, may provide a suitable treatment option. The purpose of this thesis is to investigate the feasibility of neurofeedback (NFB) for the treatment for chronic tinnitus. To achieve this goal, first, a comprehensive literature review investigating the effectiveness of existing neurofeedback treatments as well as summarizing findings of electrophysiological tinnitus studies was conducted. Main results of this article suggested that tinnitus research at this point is not yet able to identify specific biomarkers for distinct tinnitus subtypes due to a lack of study guidelines. Nevertheless, alpha/delta neurofeedback has been identified as a promising protocol to relieve and stabilize tinnitus-related symptoms (e.g., distress and loudness). Furthermore, it was concluded that the spatial resolution of electrophysiological recordings, commonly used for measuring brain activity for neurofeedback, is insufficient and needs to be improved (e.g., by combining NFB with source estimation algorithms).

Based on findings and considerations of this literature review, an extensive and well controlled clinical study was conducted. 53 patients with chronic tinnitus participated in 15 neurofeedback training sessions aiming at increasing alpha and decreasing delta activity over auditory areas. Patients have been separated into 2 groups working with traditional surface-based (NTNF) and a newer tomographic (ToNF) method for feedback generation. The second article of this thesis reports findings of the NTNF group. For this group 4 active electrodes placed on fronto-central sites on the scalp have been used for the recording of feedback-relevant frequency bands (i.e., alpha and delta). These electrodes have been chosen according to previous neurofeedback investigations that worked with the same protocol. In general, neurofeedback application was designed to be nearly identical to these former studies in order to serve as possible replication. However, an important innovation of this project was the use of individually tailored alpha-reward bands, which take interindividual differences into account. Results showed that tinnitus-related distress and loudness could be successfully reduced due to the NFB intervention. However, while the effect for tinnitus distress was found to be persistent, the opposite was true for tinnitus loudness and scores returned back to baseline 6 months after com-

pletion of the training period. Furthermore, participants were found to be successful in altering their brain activity according to the neurofeedback protocol (i.e., alpha increase and delta decrease), which suggested specific effects of this intervention.

The third article focused on the comparison between tomographic and non-tomographic feedback application. ToNF was performed with 31 active electrodes across the whole scalp and an implemented sLORETA source estimation algorithm. Results suggested that also tomographic neurofeedback is able to improve tinnitus-related symptoms and induce the intended neural alterations in primary auditory areas. However, when compared to NTNF, results of this study suggested no additional benefits of ToNF regarding symptom improvement and only partial evidence for increased spatial precision. It was thus concluded that more specific biomarkers for distinct tinnitus subtypes are urgently needed in order to develop more specific neurofeedback protocols.

Zusammenfassung

Das chronische Ohrgeräusch, Tinnitus, ist eine akustische Hörempfindung, die nicht von einem externen akustischen Signal ausgelöst wird, sondern aus fehlgeleiteten Kompensationsmechanismen im Gehirn (oft infolge einer Schädigung von Rezeptorzellen im Innenohr) entsteht. Es existiert derzeit keine wirksame Behandlung zur vollständigen Linderung von Tinnitus und viele Betroffene leiden beträchtlich unter dem konstanten Lärm im Ohr. Neuere Befunde deuten darauf hin, dass Neurofeedback, welches auf die Normalisierung von für Tinnitus typische, neuronale Aktivitätsmuster abzielt, eine geeignete Behandlungsmöglichkeit darstellen könnte. Das Ziel dieser Doktorarbeit ist es, die Wirksamkeit von Neurofeedback (NFB) für der Behandlung von chronischem Tinnitus zu untersuchen. Um dieses Ziel zu erreichen, wurde zunächst in Form einer Literaturübersicht bestehende Neurofeedback-Behandlungen sowie elektrophysiologischer Tinnitus-Studien untersucht. Die Ergebnisse dieses ersten Artikels deuten darauf hin, dass die Tinnitusforschung zu diesem Zeitpunkt noch nicht in der Lage zu sein scheint, spezifische Biomarker für verschiedene Tinnitus-Subtypen zu identifizieren. Dennoch wurde mit Alpha/Delta-Neurofeedback ein vielversprechendes Protokoll zur Linderung und Stabilisierung von Tinnitus-Symptomen (z.B. Distress und Lautstärke) gefunden. Darüber hinaus wurde der Schluss gezogen, dass die räumliche Auflösung der elektrophysiologischen Aufzeichnungen, die häufig zur Messung der Hirnaktivität für Neurofeedback verwendet werden, unzureichend ist und verbessert werden muss (z.B. durch Kombination von NFB mit Quellenschätzungsalgorithmen).

Basierend auf den Ergebnissen und Überlegungen dieser Literaturrecherche wurde eine umfangreiche und gut kontrollierte klinische Studie durchgeführt. 53 Patienten mit chronischem Tinnitus nahmen an 15 Neurofeedback-Trainingseinheiten teil, die darauf abzielten, das Verhältnis zwischen Alpha- und Delta-Aktivität in den auditorischen Arealen des Gehirns zu erhöhen. Die Patienten wurden in 2 Gruppen eingeteilt, die mit traditionellen oberflächenbasierten (NTNF) und einer neueren tomographischen (ToNF) Methode zur Erzeugung von Feedback arbeiteten. Der zweite Artikel dieser Dissertation berichtet über die Ergebnisse der NTNF Gruppe. Für diese Gruppe wurden 4 aktive Elektroden fronto-zentral auf der Kopfoberfläche zur Aufzeichnung der relevanten Frequenzbänder (Alpha und Delta) verwendet. Diese Elektroden wurden anhand von vorangegangen Neurofeedback-Studien ausgewählt, die mit dem gleichen Protokoll arbeiteten. Die Neurofeedback-Anwendung wurde ganz allgemein so konzipiert, dass sie mit diesen früheren Studien nahezu iden-

tisch war um Aussagen über eine mögliche Replikation bisheriger Resultate machen zu können. Eine wichtige Neuerung dieser Studie war jedoch die Verwendung von individuell angepassten Alpha-Bändern für das Applizieren der Belohnungsreize, womit interindividuelle Unterschiede bis zu einem gewissen Grad berücksichtigt wurden. Die Ergebnisse der Studie zeigten, dass der mit Tinnitus verbundene Distress und die Tinnituslautstärke durch die NFB Intervention erfolgreich reduziert werden konnten. Während die Wirkung bei Distress jedoch anhaltend war, kehrte die Tinnitus-Lautstärke 6 Monate nach Absolvieren des Trainings wieder auf den Ausgangswert zurück. Es konnte ausserdem gezeigt werden, dass die Teilnehmer dieser Studie ihre Gehirnaktivität erfolgreich gemäß dem Neurofeedback-Protokoll (d.h. Alpha erhöhen und Delta verringern) ändern konnten, was auf spezifische Effekte dieser Intervention hindeutete.

Der dritte Artikel dieser Doktorarbeit konzentrierte sich auf den Vergleich zwischen tomographischem und nicht-tomographischem Neurofeedback. ToNF wurde mit 31 aktiven Elektroden über der gesamten Kopfoberfläche und einem implementierten sLORETA Quellenschätzungsverfahren durchgeführt. Die Ergebnisse dieser Studie deuteten darauf hin, dass auch tomographisches Neurofeedback in der Lage ist, Tinnitussymptome zu verbessern und die beabsichtigten neuronalen Veränderungen im primären auditorischen Kortex hervorzurufen. Beim Vergleich mit NTNF zeigten die Ergebnisse dieser Studie jedoch keinen zusätzlichen Nutzen von ToNF hinsichtlich der Verbesserung von Tinnitussymptomen und eine nur teilweise eine erhöhte räumliche Präzision. Es wurde der Schluss gezogen, dass spezifischere Biomarker für verschiedene Tinnitus-Subtypen dringend benötigt werden, um spezifischere Neurofeedback-Protokolle zu entwickeln.

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Glossary

AAPB Association for Applied Psychophysiology and Biofeedback.

ACC Anterior cingulate cortex.

ADHD Attention deficit hyperactivity disorder.

ANOVA Analysis of variance.

BAI Beck's Anxiety Inventory.

BDI Beck's Depression Inventory.

BOLD Blood oxygenation level dependent.

CBT Cognitive behavioral therapy.

EC Eyes closed.

EEG Electroencephalography.

EEG-NT EEG with no task.

EEG-WT EEG with task.

EO Eyes open.

ESIT European School for Interdisciplinary Tinnitus Research.

FDT Frequency discrimination training.

FFT Fast Fourier Transform.

fMRI Functional magnetic resonance imaging.

fNIRS Functional near-infrared spectroscopy.

IAF Individual alpha frequency.

ICA Independent component analysis.

ICD-10 International Statistical Classification of Diseases and Related Health Problems, 10th revision.

ILN Infra-low neurofeedback.

MEG Magnetoencephalography.

MVPA Multi-voxel pattern analysis.

NFB Neurofeedback.

NTNF Non-tomographic neurofeedback.

PAC Primary auditory cortex.

PCC Posterior cingulate cortex.

pHC Parahippocampus.

rt-fMRI Real-time functional magnetic resonance imaging.

rTMS Repetitive transcranial magnetic stimulation.

SCL-K-9 Symptom Check List.

SCP Slow cortical potential.

SF-36 Short Form Health Questionnaire.

SLIM Synchronization by loss of inhibition modulation.

sLORETA Standardized low resolution electromagnetic tomography.

SMR Sensorimotor rhythm.

tACS Transcranial alternating current stimulation.

TCD Thalamocortical dysrhythmia.

tDCS Transcranial direct current stimulation.

THI Tinnitus Handicap Inventory.

TIN-ACT Tinnitus Assessment, Causes, and Treatment.

TINNET COST Action BM1306 'Better Understanding the Heterogeneity of Tinnitus to Improve and Develop New Treatments'.

ToNF Tomographic neurofeedback.

TQ Tinnitus Questionnaire.

TRI Tinnitus Research Initiative.

tRNS Transcranial random noise stimulation.

TSCHQ Tinnitus Sample Case History Questionnaire.

vmPFC Ventromedial prefrontal cortex.

WHO World Health Organization.

WHOQOL-BREF Short form of the WHO Quality of Life Scale.

Chapter 1

Introduction

The main goal of this thesis was to evaluate and discuss neurofeedback as a potential treatment option for chronic tinnitus patients. First, an introduction to the symptomatology of chronic tinnitus will be given. In particular, the necessary definitions and distinctions will be provided, as well as risk factors and behavioral consequences. Further, contemporary theories and models dealing with the emergence of tinnitus will be summarized, followed by a critical discussion of currently existing treatments. Secondly, neurofeedback will be introduced as a recently emerging possibility for the treatment of various psychological and neurological disorders. The methodology of neurofeedback will be explained in detail and recent developments will be addressed, before ending the chapter with elaborating on open issues as well as the aim and significance of this thesis. Empirical research performed in the scope of this project will be presented next. In particular, the results of a comprehensive literature review on existing neurofeedback protocols in tinnitus treatment (see chapter 2.1), and of the largest clinical neurofeedback training study in the field (see chapters 2.2 and 2.3) will be summarized. The empirical part will be followed by a general discussion of the findings in the context of current tinnitus research. Limitations of this thesis will be revised, and implications as well as future perspectives discussed.

1.1 Chronic Tinnitus

Tinnitus is a phenomenon that was still largely unknown in the general population about 30 years ago (Sanchez, 2014). Although even then, people complained about an odd auditory sensation, usually the morning after a noisy concert or party, few were familiar with the technical term *tinnitus*. Often the sensation was unspecifically denoted as ringing or whistling and people were relieved when the phantom noise faded away after some time. More and more, however, medical reports started to circulate about some individuals, in which the perturbing sensation persisted and that had to deal with it day after day. While at first, these reports rather served

the purpose to prevent children and adolescents from listening to loud music, tinnitus became a serious health concern in Western populations in the following years. Today, *tinnitus* is a term not only known to otologists but increasingly also to the general public. Articles in newspapers, health magazines, and TV or radio broadcasts are published dealing with prevention and possible treatments of this condition. Noisy environments, increased work and private stress as well as age-related hearing loss are assumed to contribute to this growing trend (Nondahl et al., 2012). Being an often discussed topic in the public, research in this field has also prospered and theories on possible emergence of tinnitus as well as potential treatment approaches have grown exponentially. Nowadays, this branch of research even brought forth its own scientific journal (see http://www.tinnitusjournal.com), research associations have joined forces and built organized initiatives on a European (TINNET[1], ESIT[2], or TIN-ACT[3]) and on a global level (Tinnitus Research Initiative, TRI[4]), data bases are being built (see https://www.tinnitus-database.de), and conferences are held all over the world to discuss the newest scientific insights. Despite the striking number of tinnitus-related publications, up to this day, no theory has been proposed that completely explained tinnitus emergence and no treatment has been developed that entirely alleviates its symptoms. In this chapter, the most relevant theories alongside with popular, yet insufficiently effective, treatment possibilities will be presented and discussed. Before doing so, however, important definitions and distinctions will be provided. Furthermore, prevalence of tinnitus as well as categorization in the established medical classification systems will be illuminated.

1.1.1 Definition and Classification

The term tinnitus is derived from the Latin verb *tinnire* which translates to *to ring*. Historically, first mentions date back as far as to the ancient Greeks and Egyptians (Dietrich, 2004), and since the late 1990ies, tinnitus is defined as the perception of a sound without an external sound source (P. J. Jastreboff, 1990). It is important to distinguish between the less frequent *objective* and the more common *subjective* tinnitus (Heller, 2003). Objective tinnitus can not only be perceived by the patient, but also by the medical examiner and therefore holds an identifiable (mostly vascular) origin. In contrast, the subjective type of tinnitus, also known as *tinnitus aurium*, can only be perceived by the patient and no tests or measurements exist to date to objectively quantify the ringing sensation. In addition, some researchers defined the so-called *somatosensory* tinnitus, which can be seen as a special case of

[1] http://www.tinnet.tinnitusresearch.net
[2] https://esit.tinnitusresearch.net
[3] https://tinact.eu
[4] http://www.tinnitusresearch.org

subjective tinnitus (e.g., Biesinger, Groth, Höing, & Hölzl, 2015). This sub-type is strongly related to muscle tensions in the head and neck area and the sensation can even be voluntarily altered by head or jaw movements. Another important distinction of tinnitus is related to the time perspective. It has already been mentioned that most people experience temporary acoustic phantom sensations at least once in their life (e.g., after a noisy concert). Because this percept usually fades away spontaneously, the phenomenon has been termed *sub-acute* or *transient* tinnitus (Henry, Dennis, & Schechter, 2005). If the percept persists over multiple days, the condition is generally called *acute* tinnitus, and only if the percept persists over 6 - 12 months, the tinnitus is considered to be *chronic* (Ortmann, Müller, Schlee, & Weisz, 2011). Since chronic subjective tinnitus is the topic of this thesis, the term *tinnitus* will henceforth be used synonymously.

Many epidemiological studies have already been performed to estimate prevalence numbers of tinnitus. However, due to inconsistent definitions and the use of unspecific questions (e.g., "Did you already perceive ringing in your ears?"), the estimates differ considerably. McCormack, Edmondson-Jones, Somerset, and Hall (2016) reported that the prevalence of tinnitus estimated for Western populations in different investigations varies between 5.1% and 42.7%. Two of the more commonly quoted articles in tinnitus research concerning tinnitus prevalence are the reviews by Heller (2003) and Henry et al. (2005) and the number is often limited to 5-15%. Additionally, it is often referred to the work of Shargorodsky, Curhan, and Farwell (2010), who showed that tinnitus increases with advancing age with a peak of 14.3% between age 60 and 69, or to the publication of Holmes and Padgham (2008), who estimated the same prevalence as 12%. Furthermore, a higher prevalence for men than for women is often reported (Ahmad & Seidman, 2004; Axelsson & Ringdahl, 1989; Lockwood, Salvi, & Burkard, 2002).

In the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), a medical classification system provided by the World Health Organization (WHO), tinnitus is listed in chapter VIII *Diseases of the ear and mastoid process*, H93 *Other disorders of ear, not elsewhere classified*, H93.1 *Tinnitus*. This reflects the still wide-spread misleading belief of many medical healthcare professionals that tinnitus is a sole problem of the auditory periphery. As this thesis will show, processes in the inner ear indeed seem to play a part in contributing to the emergence of the phantom percept. However, the main factors leading to its perception and chronification occur predominantly in central auditory and non-auditory areas of the human brain.

1.1.2 Risk Factors and Behavioral Consequences

A variety of risk factors have already been discussed in the tinnitus literature. Besides the above mentioned possible correlations with gender and age, stress has emerged as a potential risk factor for both, emergence and chronification, of the phantom percept (e.g., Mazurek, Haupt, Olze, & Szczepek, 2012). Additionally, a high level of noise exposure in everyday life has been identified as additional risk factor, which at least partly explains the higher prevalence for male individuals (i.e., increased probability for this group to work in noisy environments) (Nondahl et al., 2012). Furthermore, this circumstance also explains the increasing prevalence of tinnitus in the population of younger individuals as listening to loud music with in-ear headphones is very popular for this age group (Gilles et al., 2013; Sanchez et al., 2015; Williams & Carter, 2016). Apart from that, personality traits such as neuroticism (Strumila, Lengvenyte, Vainutiene, & Lesinskas, 2017), genetic factors (Bogo et al., 2017; Cederroth, Kähler, Sullivan, & Lopez-Escamez, 2017), medication such as the common Aspirin (Cianfrone et al., 2011), several otological diseases such as Ménière's disease (Baguley, McFerran, & Hall, 2013), and lifestyle factors such as smoking (Shargorodsky et al., 2010) have been discussed.

The biggest and most consistently reported risk factor for developing tinnitus, however, is hearing loss (e.g., Gopinath, McMahon, Rochtchina, Karpa, & Mitchell, 2010). On the one hand, this might explain the aforementioned correlations between of prevalence with noise exposure as well as with older age (i.e., presbycusis). Both conditions can lead to sensorineural hearing loss, a type of hearing loss that is caused by damage to inner ear receptor cells (i.e., hair cells) or the auditory nerve. However, many tinnitus sufferers do not report hearing loss (Guest, Munro, Prendergast, Howe, & Plack, 2016) and show unobtrusive hearing thresholds. To solve this conundrum, researchers suggested the use of more precise audiometric tests apart from standard pure tone audiometry, which are commonly used in medical practice (e.g., Weisz, Hartmann, Dohrmann, Schlee, & Noreña, 2006) or to investigate the condition of *cochlear synaptopathy*, also known as *hidden hearing loss* (Eggermont, 2016b; Guest et al., 2016; Knipper, van Dijk, Nunes, Rüttiger, & Zimmermann, 2013; Liberman, 2017; Omidvar et al., 2016; Paul, Bruce, & Roberts, 2016; Schaette & McAlpine, 2011). Hidden hearing loss has been explained by damaged synaptic connections between hair cells and the auditory nerve (Liberman, 2017). The auditory system usually compensates for this form of damage, however some individuals may complain about a reduced ability to detect speech in noise, a condition very well known in tinnitus patients (Gilles et al., 2016; Ivansic et al., 2017; Jagoda et al., 2018; Liberman, 2017; Valderrama et al., 2018). Therefore, it is now widely believed

that, for tinnitus to emerge, at least some form of hearing loss or ear damage has to be present whether it is manifested as the measurable sensorineural or as the more concealed hidden hearing loss (Elgoyhen, Langguth, De Ridder, & Vanneste, 2015).

When it comes to consequences of tinnitus, the list is long (for a review, see Heller, 2003; Henry et al., 2005; Holmes & Padgham, 2008, 2009). Around 1-3% of the general population (20% of tinnitus patients) suffer gravely from the intermittent percept and report considerable decreases in their quality of life (Elgoyhen et al., 2015). The most common complaints are sleep disturbances (Crönlein et al., 2016; Xu, Yao, Zhang, & Wang, 2016), concentration problems and altered cognition (Mohamad, Hoare, & Hall, 2015; Trevis, McLachlan, & Wilson, 2017), disturbed social interactions due to impaired auditory functioning (Ahmad & Seidman, 2004), and severe comorbid disorders such as depression (Dobie, 2003; Langguth, 2011) or anxiety (Pattyn et al., 2015; Ziai, Moshtaghi, Mahboubi, & Djalilian, 2017). Furthermore, many tinnitus patients report an increased sensitivity to sound, a condition generally known as *hyperacusis* (Fackrell et al., 2017; Knipper et al., 2013; Song et al., 2014). Consequences of chronic tinnitus are thus severe and costly, posing a major challenge for health care systems all over the globe (Baguley et al., 2013; Goldman & Holme, 2010). In addition, an increasingly aging population, combined with a noisy and stressful environment, will cause drastic prevalence increases of chronic tinnitus in the future (Sanchez, 2014). One of the main problems concerning the development of an effective treatment for the chronic phantom percept is that still no theory or model sufficiently unveiled the maladaptive processes of tinnitus emergence. The most relevant theories in this regard will be presented in the next section.

1.1.3 Relevant Theories on Tinnitus Emergence

Initial approaches to explain tinnitus focused entirely on the auditory periphery and considered damage to the inner ear or the auditory nerve to be the main cause for the development of the phantom percept (Eggermont, 1990; Møller, 1984). This approach is still popular today as, for example, the classification according to the ICD-10 suggests. These *peripheral models* generally explain tinnitus as a result of hyperactivity in the cochlea or auditory nerve fibers. However, first attempts to surgically treat the chronic noise by intersecting the auditory nerve failed (House & Brackmann, 1981), and as a consequence processes in the human brain moved into the focus of attention. A major contribution in this regard was the work by P. J. Jastreboff (1990) who proposed an explanatory approach that was later known as the *neuropsychological model of tinnitus*. Jastreboff provided an answer to the

question of why a relatively weak, constant signal does not undergo habituation and is perceived continuously. As it was common at this time, also Jastreboff located the generation of this signal primarily in the auditory periphery as a result of auditory receptor or nerve damage. However, he is considered to be one of the first in this research field who suggested the importance of central processes in auditory cortex areas, the limbic system, and the prefrontal cortex for tinnitus emergence. He credited these brain regions a major role in the detection and affective evaluation of the tinnitus signal, which is necessary for the persistent perception to arise without habituation.

Later models built upon this general idea of Jastreboff but localized the source of hyperactivity in subcortical structures rather than the auditory periphery. The *central gain model* proposed by Noreña (2011), for instance, states that cochlear damage leads to increased activity in all higher levels of the auditory pathway from the cochlear nucleus, the inferior colliculus in the midbrain, the medial geniculate body of the thalamus, to the primary and secondary auditory areas in the neocortex (see Figure 1). The author considered this hyperactivity to be the result of an increased central gain (i.e., neuronal sensitivity) that emerges due to attempts to compensate for reduced sensory inputs so that a stable mean firing, neural coding efficiency, and thus auditory functioning are preserved. According to the central gain model, this attempt of the brain, however, also amplifies *neural noise*, and tinnitus is perceived as a result.

Other theoretical approaches to explain tinnitus focused more and sometimes exclusively on processes in primary auditory cortex (PAC) areas. The idea behind these models is that every sound perception, whether of external or internal origin, necessarily arises in the part of the brain where the auditory pathway terminates and sounds are finally processed and perceived. Neurobiological studies found that every cochlear hair cell receptor is sensitive to stimulation with a specific frequency in sound waves (determining the pitch of the perceived sound) and relays this information in form of neuronal activity to the auditory cortex (Ruggero, 1992). Moreover, animal studies have shown that the neurons in Heschl's gyri (also referred to as transverse temporal gyri), where the PAC is located, are arranged in systematic maps, receiving input from these cochlear receptors and are thus sensitive to distinct sound frequency ranges (Reale & Imig, 1980). Therefore, a *tonotopic map* has been credited to the PAC, similarly to the *somatotopic map* in the somatosensory cortex. As a consequence, several scholars considered tinnitus as an analogy of phantom limb pain (e.g., Mühlnickel, Elbert, Taub, & Flor, 1998). This phenomenon occasionally occurrs in amputation patients who still report pain in the

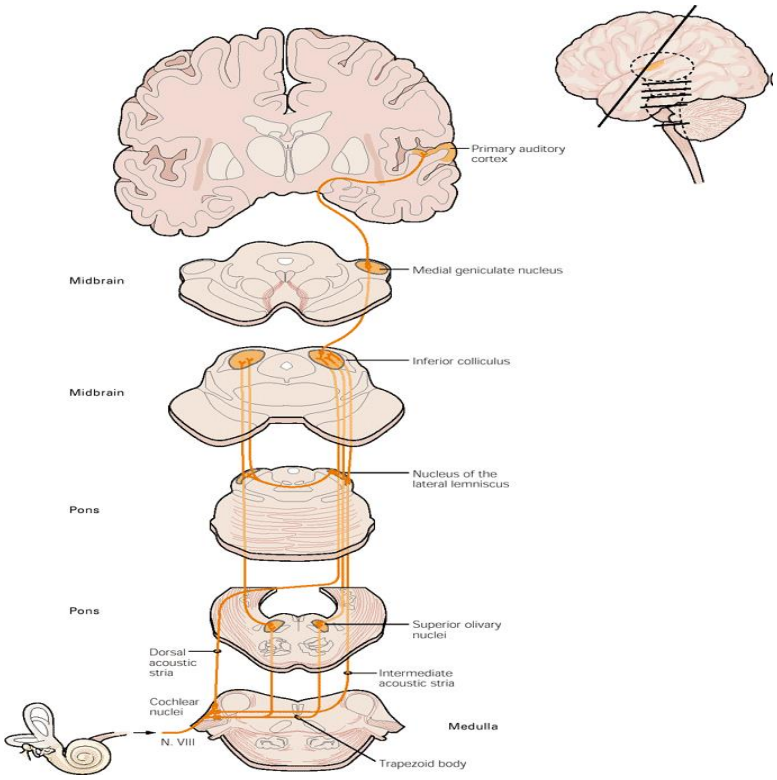

Figure 1: The central auditory pathway from the cochlea to the primary auditory cortex (Kandel et al., 2013, p. 685).

missing limb and was considered, for a long time, as one of the biggest mysteries in neuroscience (Sherman, Arena, Sherman, & Ernst, 1989). Meanwhile, however, it has been shown that plastic reorganization processes are responsible for this phantom sensation (Ramachandran, Rogers-Ramachandran, & Stewart, 1992). Amputation of a certain part of the body causes cells in primary somatosensory areas that used to be connected with the missing limb to be input deprived, which initiates an integration process with cells of surrounding receptive fields. This process is believed to generate random spontaneous firing among the acquired neurons, which is then perceived as pain for the individual (Flor et al., 1995). Similarly, it was found that, when auditory receptor cells in the inner ear are damaged, corresponding neurons on the tonotopic map are input deprived and cortical reorganization is initiated (Eggermont & Roberts, 2004). Therefore, increased spontaneous firing due to expansion of lesion edge frequencies has been considered to be responsible for the auditory analogue of phantom perceptions, i.e. tinnitus.

While these considerations might explain the typical perception of tinnitus in the frequency range of hearing loss (usually as a high-pitched ringing sound), some inconsistencies remain. For instance, no correlation between the extent of tonotopic map reorganization and intensity of the phantom percept has been observed (Weisz, Voss, Berg, & Elbert, 2004; Weisz, Wienbruch, Dohrmann, & Elbert, 2005)

as it was the case for the somatosensory equivalent (Flor et al., 1995). Furthermore, most evidence supporting this theory was gathered on animal models and it is highly controversial to assume similar processes or PAC organization in the human brain (Eggermont, 2016a; Langers, 2014). Working with human tinnitus patients, many research groups failed to find any evidence for tonotopic map reorganization, suggesting that these processes might rather be a reaction to hearing loss and not a prerequisite for tinnitus emergence (Ghazaleh et al., 2017; Langers, De Kleine, & van Dijk, 2012).

Apart from increased spontaneous firing rates in different parts of the auditory pathway, *neural synchrony models* have been proposed (Eggermont & Roberts, 2004; Noreña & Eggermont, 2003; Seki & Eggermont, 2003; Weisz, Dohrmann, & Elbert, 2007; Weisz, Moratti, Meinzer, Dohrmann, & Elbert, 2005). These models do not consider a solely quantitative enhancement of brain activity but rather changes in synchronous firing patterns of various cell assemblies to be vital for tinnitus genesis. This idea goes back to the work of Singer (1993) who investigated *binding processes* in the context of visual input integration. He showed that integration of sensory input is closely related to different neuronal networks in the brain synchronizing their firing patterns so that unified percepts can be formed. Electrophysiological recordings with electroencephalography (EEG) or magnetoencephalography (MEG) are well suited for the measurement of these processes as the recorded signal represents both, excitatory and inhibitory post-synaptic potentials (Weisz, Dohrmann, & Elbert, 2007). The derived wave signal can be decomposed into its frequency components (e.g., with Fast-Fourier Transforms, FFTs) indicating oscillatory, rhythmic, and thus synchronized activity in the brain (Michel & Koenig, T., Brandeis, D., Gianotti, L., & Wackermann, J., 2009). These components are usually categorized into distinct frequency bands: delta (0.5–4 Hz), theta (4.5–8 Hz), alpha (8.5–12 Hz), beta (12.5–35 Hz), and gamma (35.5–80 Hz).

Oscillations in M/EEG brain waves in the fast-paced gamma rhythm have been claimed to reflect binding processes in the human brain (Singer, 1993). Since spontaneously emerging gamma oscillations have repeatedly been found to be predominant over auditory areas of tinnitus patients (Ashton et al., 2007; van der Loo et al., 2009; Weisz, Müller, et al., 2007), this rhythm has been credited a pivotal role for the chronic phantom percept. Apart from these findings, resting-state M/EEG studies were able to identify a variety of other rhythmic abnormalities in the brains of tinnitus patients (for a review, see Adjamian, 2014; Schlee et al., 2009), in particular decreased resting-state alpha alongside with increased delta oscillations. Llinás, Ribary, Jeanmonod, Kronberg, and Mitra (1999) attributed the increased occurrences

of delta oscillations to disturbances in thalamocortical feedback loops, which they previously identified as playing an essential role in conscious perception (Llinás, Ribary, Contreras, & Pedroarena, 1998). When thalamic cells are deprived from (auditory) input (i.e., are in a state of constant *deafferentation*) spontaneous firing in a slow-wave delta mode arises. Due to the aforementioned feedback loops, this firing pattern is further relayed to cortical areas where the persistent slow-wave state induces fast gamma oscillations, a process Llinás termed the *edge effect* (Llinás et al., 1999; Llinás, Urbano, Leznik, Ramírez, & van Marle, 2005). In addition to this *thalamocortical dysrhythmia* (TCD) model, the group around N. Weisz established what is nowadays known as the *synchronization by loss of inhibition modulation* (SLIM) model (Weisz, Dohrmann, & Elbert, 2007). To explain the uncontrolled gamma firing, the authors proposed a deafferentation-induced release of inhibition, which can be measured by a decreasing of cortical alpha activity (Weisz, Moratti, et al., 2005; Weisz, Müller, et al., 2007). Since these models alongside with tinnitus-specific EEG patterns are subject to comprehensive discussion in section 2.1, they will not be further discussed here. It shall briefly be mentioned at this point, however, that many studies have failed to corroborate gamma as the neuronal correlate of the tinnitus tone (e.g., Sedley & Cunningham, 2013; Sedley et al., 2012) or did not find evidence for tinnitus-specific frequency alterations at all (e.g., Pierzycki, McNamara, Hoare, & Hall, 2015; Zobay & Adjamian, 2015).

Besides auditory areas in the human brain, regions outside of the auditory cortex were subject of investigations in tinnitus research. Rauschecker, Leaver, and Mühlau (2010) considered the limbic system, in particular amygdala, nucleus accumbens, and ventromedial prefrontal cortex (vmPFC), to be involved in an inhibitory gating mechanism. They proposed that these structures, together with thalamic reticular nuclei, are part of a noise-cancelling feedback loop, which is able to protect the auditory central system from any unpleasant sounds under normal conditions. If this inhibitory mechanism, however, fails (e.g., because descending projections from the vmPFC are damaged), tinnitus is perceived (Rauschecker, May, Maudoux, & Ploner, 2015). According to this *frontostriatal gating model*, the tinnitus signal is not sufficiently suppressed and, therefore, reaches consciousness.

An even more comprehensive framework was suggested by De Ridder et al. (2014) building upon *global workspace models* of consciousness (Baars, 1987). According to these considerations almost the whole brain is eventually involved in tinnitus emergence as different aspects of the chronic phantom sound are proposed to be coded in distinct parallel overlapping (sub-) networks summarized in Figure 2. The authors identified a *tinnitus core network* encompassing the minimal areas in the

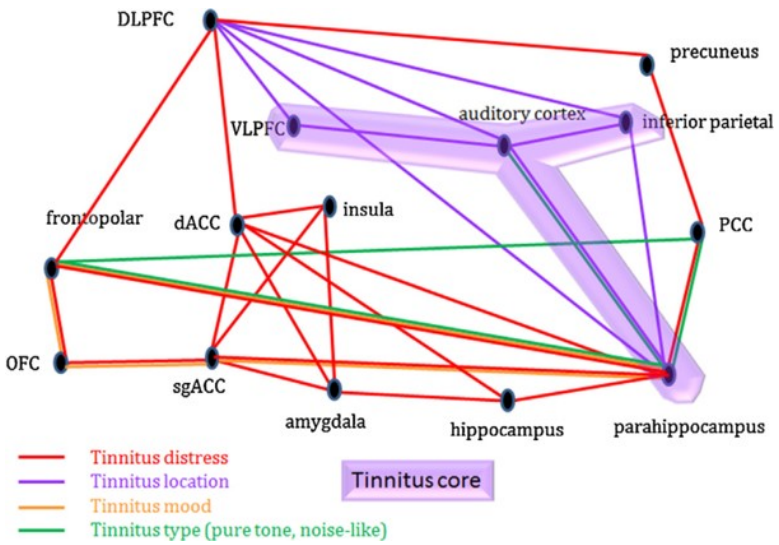

Figure 2: Tinnitus core- and sub- networks (De Ridder et al., 2014, p. 27). dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; VLPFC, ventrolateral prefrontal cortex.

brain responsible for conscious perception of the tinnitus sound. De Ridder believes the tinnitus sound to be generated due to processes that *fill in* missing auditory information actively in a Bayesian way (De Ridder, Vanneste, & Freeman, 2012). According to this view, the brain constantly tries to make efficient predictions about its environment and updates them based on sensory feedback in order to reduce uncertainty (Friston, Kilner, & Harrison, 2006). A lack of auditory input due to inner ear receptor damage limits the amount of information available for the brain to make successful predictions. Due to increased prediction errors and uncertainty, the brain initiates processes to compensate for this missing sensory information (e.g., increasing cortical excitability or widening auditory receptive fields). However, when the amount of receptor loss is too high and the brain is thus unable to acquire the necessary data via neuronal reorganization processes, the missing info might be obtained from memory (De Ridder, Elgoyhen, Romo, & Langguth, 2011). This is why the parahippocampus (pHC), a brain structure strongly involved in memory processes, is crucial in De Ridder's approach and an important part of his proposed core network (see Figure 2). However, processes in this core network are not enough for conscious perception of the phantom sound to arise. Following the ideas of P. J. Jastreboff (1990), De Ridder believed cognitive and emotional aspects of tinnitus to be equally important and claimed that the evoked signals never reach consciousness if they are not considered to be salient and behaviorally relevant. Therefore, activity in the tinnitus core has to be integrated into other networks coding salience and emotional valence of the initial tinnitus signal (see Figure 2) so that a conscious percept can be generated (De Ridder et al., 2014).

Recently all the previously mentioned models have been comprehensively summarized by William Sedley (see Figure 3). Sedley listed the shortcomings of each of these models and claimed that they are not able to fully explain tinnitus genesis, even when considered complementary (Sedley, Friston, Gander, Kumar, & Griffiths, 2016). Furthermore, the author proposed a new model on the basis of *predictive coding*. According to this view, spontaneous activity in the auditory pathway (the *tinnitus precursor*) is normally compared against the prevailing percept of silence and therefore ignored. If the precision of this precursor, however, increases (i.e., top-down prediction errors decrease), which Sedley claimed to be linked to the rise of postsynaptic gains, tinnitus is perceived. In combination with attentional processes, it is possible that the default prediction is reset to expect tinnitus (instead of silence) which leads to chronification of the phantom percept (Sedley et al., 2016). Whether or not this model is plausible and fruitful for understanding the processes leading to chronic tinnitus remains to be seen and is currently subject of ongoing research projects.

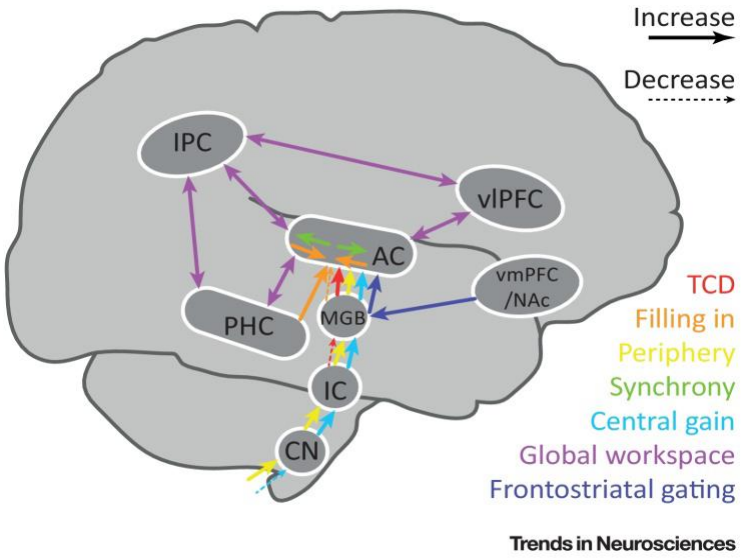

Figure 3: Overview of brain regions involved in tinnitus generation according to existing tinnitus models (Sedley et al., 2016, p. 3). AC, auditory cortex; CN, cochlear nucleus; IPC, inferior parietal cortex; MGB, medial geniculate body; NAc, nucleus accumbens; PHC, parahippocampus; vlPFC, ventrolateral prefronal cortex; vmPFC, ventromedial prefrontal cortex.

To summarize, a variety of approaches have already been postulated aiming at shedding light in the underlying processes of tinnitus emergence (for an overview, see Figure 3). It is important to note that most of these models build on each other and, therefore, are not to be considered mutually exclusive. A problem of many tinnitus

theories, however, is the fact that they did not sufficiently consider the heterogeneity of the phenomenon and the inter-individual differences between patients (Landgrebe et al., 2010; Langguth, Kreuzer, Kleinjung, & De Ridder, 2013; van den Berge et al., 2017). The COST Action program TINNET, a network of various tinnitus research facilities all over Europe, has thus declared the identification of distinct tinnitus subtypes to be crucial for tinnitus understanding and treatment.

1.1.4 Tinnitus Treatment

Despite the growing knowledge about tinnitus origin, an effective treatment to utterly cure the chronic phantom sensation has not yet been developed. Pharmacological approaches have been considered: apart from the most intensely studied *Lidocaine*, a local anesthetic (Trellakis, Lautermann, & Lehnerdt, 2007), various benzodiazepines (Johnson, Brummett, & Schleuning, 1993) and antidepressants (Oishi et al., 2010), other neurohormones such as oxytocin (Azevedo et al., 2017) or melatonin (Abtahi, Hashemi, Mahmoodi, & Nilforoush, 2017), and the herbal extract *gingko biloba* (Ernst & Stevinson, 1999; Mahmoudian-Sani, Hashemzadeh-Chaleshtori, Asadi-Samani, & Yang, 2017) have been subject of pharmaceutical studies. However, none of these medicaments has been proven to exceed placebo effects in their effectiveness to reduce tinnitus symptoms and, therefore, no drug has yet been legally approved for the treatment of chronic tinnitus (Langguth, Elgoyhen, & Cederroth, 2018).

The fact that no miracle drug has yet been discovered for tinnitus remedy and insufficient knowledge of many medical experts about latest research findings provides a huge challenge for tinnitus sufferers. Far too often patients are simply advised that tinnitus is untreatable and they had to live with it for the rest of their lives (Holmes & Padgham, 2009). This leaves many of them in a sense of increasing helplessness as they feel left alone and not taken seriously by medical specialists, which oftentimes even enhances the negative effects on well-being and quality of life. As a result, they seek help in a variety of alternative, expensive, and mostly virtually ineffective treatment options. Fernandes (2017) thus eloquently calls tinnitus patients to be a "convenient target for multiple and unconventional therapies" (p. 175). Nevertheless, research has been intensified over the last decades, fueling hope within the tinnitus community that relief might be in sight. Increasing scientific knowledge and the emergence of new theoretical models about tinnitus, as presented in section 1.1.3, have led to a better understanding and development of innovative treatment strategies using state-of-the-art technologies. The most promising approaches developed so far constitute psychotherapeutic interventions, attempts to restore auditory input

with hearing aids and acoustic stimulation, and neuromodulation and -stimulation techniques (see Figure 4). Selected methods will be presented and critically evaluated in the following paragraphs.

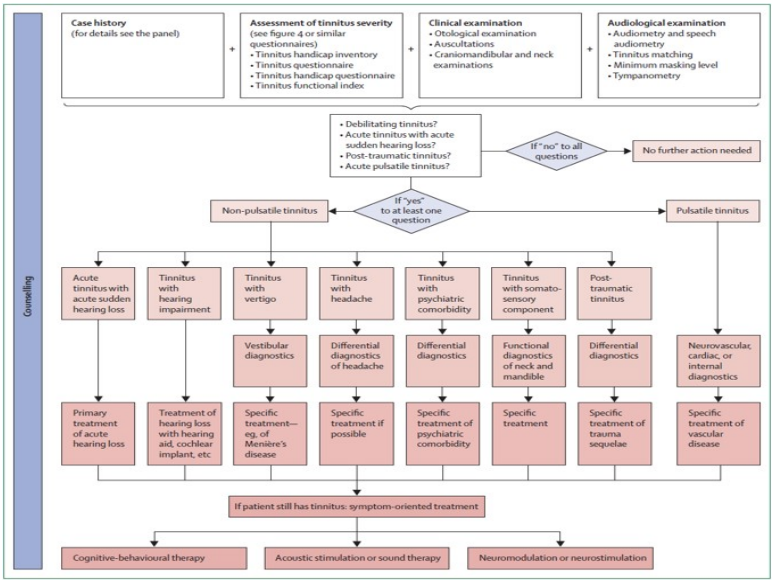

Figure 4: Proposed scheme for diagnosing and treating chronic tinnitus patients (Langguth et al., 2013, p. 923).

1.1.4.1 Psychotherapy

Proper psychoeduction or counselling about tinnitus and its underlying causes often significantly improve quality of life for many tinnitus sufferers (Langguth et al., 2013). False beliefs, e.g. that tinnitus reflects a warning for a concealed underlying disease, cause intense distress and destructive thoughts for many affected individuals. Educating patients about auditory and neuronal origins of the phantom percept can thus help in understanding that tinnitus is not a terrible disease but rather a symptom that emerged in the context of a well-intended attempt of the brain to maintain functionality. Counselling strategies further aim at supporting patients in improving habituation to the percept and in coping with its potential behavioral, social and health-related consequences. Jastreboff developed the so-called *tinnitus retraining therapy* by combining these counselling methods with relaxation techniques and sound therapy (P. J. Jastreboff & Jastreboff, 2001). This approach aims at changes in emotional reactions to the tinnitus sound and currently enjoys great popularity in many tinnitus-specialized treatment centers. However, due to a lack of randomized control trials, the effectiveness of this approach is yet unproven and final conclusions about its therapeutic use should not be made (Phillips & McFerran, 2010).

In addition, tinnitus treatment has been implemented in *cognitive behavioral therapy* (CBT), which has shown to be very helpful when it comes to changing maladaptive cognitions, develop functional coping strategies, and thus showing patients that a good and successful life is possible even with tinnitus (Langguth et al., 2013). CBT interventions mainly focus on psychological models of tinnitus emergence and maintenance, according to which sound perception leads to negative thoughts and emotional appraisal processes that can cumulate in a vicious circle of more arousal, more distress and more attention towards the percept (e.g., McKenna, Handscomb, Hoare, & Hall, 2014). Specific manuals for the cognitive-behavioral treatment of chronic tinnitus have already been established (e.g., Kröner-Herwig, Jäger, & Goebel, 2010). Taken together, these guides suggest combining tinnitus counselling with mindfulness training, relaxation techniques, imparting of strategies for attentional control and stress management, acceptance and commitment therapy, or behavioral modification. CBT thus enjoys great popularity in tinnitus treatment nowadays and several empirical studies verified beneficial effects on tinnitus-related distress (Brüggemann et al., 2018; Cima et al., 2012; McKenna, Marks, Hallsworth, & Schaette, 2017; McKenna, Marks, & Vogt, 2017).

1.1.4.2 Hearing Aids and Acoustic Stimulation

In the case of tinnitus patients with excessive hearing loss, hearing aids (Cabral et al., 2016; Trotter & Donaldson, 2008) or cochlear implants (Baguley & Atlas, 2007; Holder, O'Connell, Hedley-Williams, & Wanna, 2017; Song, Punte, De Ridder, Vanneste, & van de Heyning, 2013) have been successfully used to compensate for the loss of auditory input. However, simple sound amplification seems to be limited for the perception of higher frequencies, which are usually impaired in tinnitus patients, and generally fails to alleviate symptoms when tinnitus mechanisms are already detached from its origin in the auditory periphery (so-called *decompensated tinnitus*) (Langguth et al., 2013). Hearing aids have also been combined with sound generators that aim at masking the tinnitus tone with environmental sounds or white noise (Durai & Searchfield, 2017; Searchfield, Durai, & Linford, 2017; Sereda, Davies, & Hall, 2016). In this case, the produced sound is proposed to overlay the tinnitus tone and to have a relaxing effect on the user. Even though these devices are very popular, and can also be used without a hearing aid device (e.g., in form of smartphone apps), their usefulness is controversial since no controlled study yet showed their effectiveness (Hoare, Kowalkowski, Kang, & Hall, 2011). Apart from stimulation with nature sounds or white noise, other groups tried to make use of music for tinnitus treatment. A research group from Heidelberg, for instance, developed a therapy concept that combined relaxing background music with tinnitus counseling and voice training techniques (resonance training and tone imitation)

(Argstatter, Grapp, Plinkert, & Volker Bolay, 2012). For this *Heidelberg Neuro-Music Therapy* some potential benefits for tinnitus-related distress alongside with possibly induced neuronal changes have been reported (Argstatter, Grapp, Hutter, Plinkert, & Bolay, 2012; Krick, Argstatter, Grapp, Plinkert, & Reith, 2017a, 2017b; Krick et al., 2015) but more controlled studies are needed to prove its effectiveness.

With regard to *acoustic stimulation*, more elaborated approaches make use of individually tailored methods. For these interventions the individual pitch of the tinnitus percept is generally determined by (pseudo-) objective audiometric matching procedures. Specifically, the treatment established by the group around Christo Pantev has attracted attention. They used so-called *notched* music, in which the individual tinnitus frequency was priorly removed from the frequency spectrum (Okamoto, Stracke, Stoll, & Pantev, 2010; Pantev, Okamoto, & Teismann, 2012; Wunderlich et al., 2015). This method was developed to evoke lateral inhibition processes in brain areas adjacent to the tinnitus frequency on the tonotopic map, and thus to help suppressing the tinnitus tone. It has indeed been shown that this intervention leads to stable reductions of tinnitus volume and less evoked activity in auditory areas corresponding to the tinnitus frequency (Okamoto et al., 2010). A similar treatment approach was suggested with the *Neuromonics* treatment, a procedure that combined tinnitus counselling with acoustic stimulation consisting in music enriched with an individually adapted broadband signal (similar to white noise), which was supposed to mask an individual's tinnitus (Davis, Paki, & Hanley, 2007; Goddard, Berliner, & Luxford, 2009). Furthermore, other auditory approaches exist that used tones instead of music to stimulate the central auditory system. The *acoustic coordinated reset* method developed in Jülich by Peter Tass, for instance, used short sound stimuli above and below the individual tinnitus pitch to initiate cortical reorganization processes (Tass, Adamchic, Freund, von Stackelber, & Hauptmann, 2012). Some evidence was indeed found that this form of stimulation leads to a reduction of tinnitus loudness and related distress compared to a placebo-control group. In addition, changes in neuronal oscillation patterns acquired with EEG were reported (Adamchic, Langguth, Hauptmann, & Tass, 2014; Adamchic, Toth, Hauptmann, & Tass, 2014; Adamchic et al., 2017). Finally, it shall be mentioned that apart from pure tones, stimulation with frequency- and amplitude modulated sounds, which have been shown to temporally suppress the tinnitus percept (an effect generally termed *residual inhibition*), is currently subject of investigation (Neff et al., 2017; Reavis et al., 2012).

To sum up, several acoustic stimulation attempts discussed here have showed promising results. In general, approaches that work with individually adjusted stim-

uli aiming at inducing cortical reorganization have proven to be more fruitful than unspecific music or masking treatments. However, as mentioned in section 1.1.3, an important consideration for these approaches is the fact that tonotopic organization of the human PAC is far from certain and cortical reorganization processes are not necessary for tinnitus emergence. Furthermore, many tinnitus sufferers do not perceive a single tone as tinnitus but rather report unspecific noise, multiple tones at once, or a percept whose pitch changes constantly. For the same reason audiometric matching procedures developed to determine an individual's tinnitus pitch objectively have been shown to be far from reliable and replicable (e.g., De Ridder, Congedo, & Vanneste, 2015). Hence, whether acoustic stimulation techniques will find a way to be established as effective tinnitus treatment methods remains to be seen.

1.1.4.3 Neuromodulation

Some of the aforementioned stimulation approaches have been designed to trigger changes on a neuronal level indirectly. In this paragraph, however, *direct* neuromodulation approaches will be discussed. These techniques have the major advantage of implementing (and thus also testing) new evidence of neuroscientific tinnitus studies. Direct neuromodulation approaches are categorized into non-invasive and invasive methods. For invasive brain modulation techniques, electrodes are inserted through the skull and neural stimulation performed extradurally on the brain surface (De Ridder & Vanneste, 2014; De Ridder, Vanneste, Kovacs, et al., 2011) or inside the cortex (*deep brain stimulation*) (Cheung & Larson, 2010; De Ridder, Joos, & Vanneste, 2015; De Ridder, van der Loo, et al., 2011) over auditory or other brain areas. This direct implantation of electrodes into the brain leads to high accuracy of the intended stimulation. However, the invasive nature of this intervention limits its scope of application as it is generally only performed in patients being prepared for neurosurgery for other reasons (e.g., epileptic patients). Even though improvements of tinnitus symptoms have been reported, the risks attached with neurosurgical procedures are still estimated too high to justify invasive stimulation as a general tinnitus treatment (Peter & Kleinjung, 2018).

An example of a non-invasive approach, which aim at inducing changes in the brain without penetrating skin or tissue, is *repetitive transcranial magnetic stimulation* (rTMS). With this technique, electromagnetic impulses are applied to the scalp that modulate neuronal activity by changing cortical excitability. Low-frequency rTMS aiming at reducing activity over temporal or temporoparietal brain areas has intensely been tested (also in combination with other simultaneous stimulation sites)

for tinnitus treatment (De Ridder, Song, & Vanneste, 2013; De Ridder, Vanneste, Kovacs, et al., 2011; Folmer et al., 2015; Kreuzer et al., 2016; Kreuzer et al., 2017; Landgrebe et al., 2017; Langguth et al., 2008; Londero, Bonfils, & Lefaucheur, 2017; Poeppl et al., 2017; Schecklmann et al., 2015; Weisz, Lüchinger, Thut, & Müller, 2012). Even though in some of these studies relief has been achieved for tinnitus patients, the effect of rTMS has generally been shown to be unspecific and only temporary (Peter & Kleinjung, 2018).

Other non-invasive neuromodulation attempts used electrical stimulation applied to the head surface. Electrodes placed on the scalp stimulate the cortex with a relatively weak and thus not directly perceivable electric current. First, *transcranial direct current stimulation* (tDCS) is typically used for inducing general excitation or inhibition effects of the underlying cells depending on the direction of current flow. Second, *transcranial alternatic current stimulation* (tACS) or *transcranial random noise stimulation* (tRNS) are applied to interact with the rhythmic firing of neurons (e.g., to increase the amount of alpha waves). Several studies have used these techniques to evaluate their efficacy for chronic tinnitus treatment. In this context, some studies that applied tDCS over temporal areas (Abtahi et al., 2018; Shekhawat & Vanneste, 2017; Vanneste & De Ridder, 2011) were able to find beneficial effects while other publications (e.g., Y. Wang et al., 2018) came to opposite conclusions. Comparisons between tACS and tRNS have shown that only the latter method leads to promising effects when it is used for modulation of alpha activity over auditory areas (Claes, Stamberger, van de Heyning, De Ridder, & Vanneste, 2014; Joos, De Ridder, & Vanneste, 2015). However, more research is needed in order to establish electrical brain stimulation as tinnitus treatment.

Also *neurofeedback* is seen as a form of non-invasive neuromodulation procedure. Since this thesis focuses greatly on this technique, it will be presented in more detail in the next section. In the end of this summary about tinnitus treatment possibilities, however, the increasing popularity of combining different treatment methods shall briefly be mentioned. Some researchers, for instance, paired acoustic with electrical stimulation with promising results (Henin, Fein, Smouha, & Parra, 2016; Mohsen, Mahmoudian, Talebian, & Pourbakht, 2018; Shekhawat, Kobayashi, & Searchfield, 2015). Furthermore, the application of tones has been combined with (invasive or non-invasive) stimulation of the vagus nerve, which is suggested to promote neuroplastic effects of the simultaneous applied acoustic stimuli. (Tyler et al., 2017; Vanneste, Martin, Rennaker, & Kilgard, 2017). Since it seems unlikely that some form of treatment single-handedly cures tinnitus, combined approaches are on the rise, which will be further discussed in chapter 3.

1.2 Neurofeedback

Neurofeedback (NFB), also known as *Neurobiofeedback* or *brainwave biofeedback*, is a neuromodulation technique which actively involves individuals in effecting the desired changes in their brain functionality. Similarly to the aforementioned neuromodulatory methods, changes in the brain are directly targeted. However, in the process of NFB, no external passive stimulation is applied but neuronal activity is simply measured and certain aspects of it visualized so that subjects are able to directly perceive their brain processes in real-time. Visualization generally follows the principles of *operant conditioning* (Skinner, 1938) where desired changes in brain activity evoke a rewarding feedback and vice versa. Following this procedure, subjects gradually learn how to voluntarily modulate their own neuronal activity so that the most desirable feedback is achieved and displayed.

Feedback application has made enormous advances over the years. Starting from simple visual feedback stimuli (e.g., rectangles moving up and down on the screen in accordance with the measured neural activity), newer methods allow for the use of auditory or tactile feedback. Furthermore, great effort has been devoted to making the feedback more pleasant, involving, and thus easier to follow for a longer time period. Today, neurofeedback is often implemented into computer games where subjects control certain aspects of a simulation (e.g., the speed of a racing car) with their own brain activity. Due to these technological advances, its non-invasive nature, virtually complete absence of side effects, its relatively low costs, and its easy handling, neurofeedback has become an extremely popular intervention method in the last decades. The biggest advantage of neurofeedback over other neuromodulation techniques, however, is that during training patients often experience substantial amounts of self-efficacy. Many affected individuals start to realize that they are actively contributing in improving their own situation and are not simply involved in passive treatment or therapy. Neurofeedback thus provides the optimal combination of self-induced learning and direct modulation of neuronal activity, which makes it one of the most promising forms of neuroscientific intervention methods to date.

1.2.1 Origin and Development

As popular as it is now, the discovery of neurofeedback was actually due to a happy coincidence. Sterman and Wyrwicka (1967) were working on operant conditioning in cats, which they trained in pulling a lever to receive food rewards. The application of an acoustic stimulus was introduced during which the cats did not receive food

rewards, despite pulling the lever. The cats had to learn to wait until this tone was not perceived anymore to activate the mechanism. The authors were interested in brain processes during this waiting period and thus simultaneously recorded EEG activity in the awake cats. They noticed previously unknown EEG spindles over the cats' primary motor- and sensory areas in a frequency range between 12 and 15 Hz which they then termed *sensorimotor rhythm* (SMR). In a follow-up study, they changed the setup of the study, with the presence or absence of these spindles being the reward-depending element (Wyrwicka & Sterman, 1968). Whenever the cats were able to produce these SMR bursts, they were rewarded with food. The authors reported that the cats were indeed able to produce this EEG rhythm, suggesting a learning effect for this electrophysiological correlate. Later, the same group was working on a different project for the space agency NASA, for which they were asked to investigate the effects of exposition to monomethylhydrazine, a component of rocket-engine propellant (Sterman, LoPresti, & Fairchild, 1969). Again, they used cats as subjects and showed that certain doses of monomethylhydrazine led to epileptic seizures. More interestingly, however, the authors noticed that the seizures were significantly delayed or even absent in those animals that were previously used in the aforementioned SMR training study. Thus, they concluded that SMR neurofeedback training may be useful in the treatment of epilepsy and started systematic studies in humans (Sterman & Friar, 1972).

After these first experiments, SMR neurofeedback was intensely tested in the context of epilepsy and has repeatedly generated highly promising results (e.g., J. F. Lubar & Bahler, 1976; Sterman & Egner, 2006). The training of SMR has been found to lead to improved control over excitation of the somatosensory system and was consequently also used for the treatment of other symptoms, such as hyperactivity and impulsivity, major components in attention deficit hyperactivity disorder (ADHD) (e.g., T. Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003). As a result, neurofeedback research picked up speed and has now become an integral part of neuroscientific intervention research.

1.2.2 Popular Neurofeedback Paradigms

Apart from SMR, also other features in EEG recordings have been used for neurofeedback paradigms. The most commonly used protocols in this regard involve training of standard frequency bands (i.e., delta, theta, alpha, beta, and gamma). With this form of training, typically one or more frequency bands are set to be rewarded, while others are set to evoke negative feedback making training of spe-

cific ratios between two or more frequency bands possible (e.g., Arns et al., 2016). Furthermore, the training of *slow cortical potentials* (SCPs) (Rockstroh et al., 1993; Strehl et al., 2017) and its similar form *infra-low neurofeedback* (ILN) (Legarda, McMahon, Othmer, & Othmer, 2011; Vanhatalo et al., 2004) have gained increasing popularity in neurofeedback practices. Both training methods aim at altering the general excitability over the whole cortex, but to date, hardly any controlled studies exist that could prove their effectiveness. In addition, *z-score neurofeedback* has been developed. In this method, training frequencies of an individual patient are chosen according to resting-state EEG data, which is compared to a normative, healthy, and age-matched database prior to training with the goal of normalizing deviations to this norm-group (Thatcher, 2010). Also evoked (in contrast to spontaneous) potentials have been implemented in neurofeedback paradigms. Rieger, Rarra, Diaz Hernandez, Hubl, and Koenig (2018), for instance, used this method to diminish the auditory *N100* amplitude to find a treatment against verbal hallucinations in schizophrenic patients. Finally, new approaches aim at altering *microstates* (Diaz Hernandez, Rieger, & Koenig, 2016; Michel & Koenig, 2017), connectivity between different brain sites (D.-Y. Kim, Yoo, Tegethoff, Meinlschmidt, & Lee, 2015; Mottaz et al., 2015; Ramot et al., 2017; Yamashita, Hayasaka, Kawato, & Imamizu, 2017) or distinct patterns of brain activity obtained with machine learning techniques such as multi-voxel pattern analysis (MVPA) (deBettencourt, Cohen, Lee, Norman, & Turk-Browne, 2015; Watanabe, Sasaki, Shibata, & Kawato, 2017).

Despite EEG being by far the most popular method to detect brain activity used for neurofeedback application, recently also other neuroscientific measurement methods have been combined with this form of brain training. MEG (Okazaki et al., 2015), functional near-infrared spectroscopy (fNIRS) (Kober, Hinterleitner, Bauernfeind, Neuper, & Wood, 2018), invasive options with implanted electrodes such as the so-called *Brain TV* (Corlier et al., 2016; Lachaux et al., 2007; Petitmengin & Lachaux, 2013), and the popular brain imaging technique *functional magnetic resonance imaging* (fMRI) have been used to record feedback-relevant features in neuronal activity. FMRI is an indirect measure of neuronal activity which is able to capture different magnetic properties of oxygenated and deoxygenated blood in the brain (blood oxygenation level dependent; BOLD) which allow conclusions about neuronal activity in certain regions of the brain. The main advantage of this method is the high spatial resolution, meaning that fMRI is able to predict the location of neuronal activity relatively precisely. However, this procedure does not come without limitations as it, for instance, fails to adequately capture fast fluctuations in brain activity, since the measured signals only appear several seconds after neurons have actually been active. Further disadvantages are noisiness and narrowness of

the scanner, which can be uncomfortable for patients and thus inconvenient for the application of neurofeedback. Nevertheless, fMRI has been increasingly used with neurofeedback and is, in this context, commonly referred to as *real-time fMRI* (rt-fMRI) (Birbaumer, 2006; deCharms, 2008; Sulzer et al., 2013; Thibault, MacPerson, Lifshitz, Roth, & Raz, 2018; Watanabe et al., 2017).

1.2.3 Application of Neurofeedback Training

Neurofeedback has been tested for the treatment of many psychological and neurological disorders. Best treatment effects have been found for ADHD, where multiple studies showed support for specific treatment effects (Alegria et al., 2017; Arns et al., 2016; Bazanova, Auer, & Sapina, 2018; T. Fuchs et al., 2003; Geladé et al., 2018; Gevensleben et al., 2009; Lofthouse, Arnold, Hersch, Hurt, & DeBeus, 2012; J. F. Lubar, Swartwood, Swartwood, & O'Donnell, 1995; Monastra, Monastra, & George, 2002; Moreno-García, Meneres-Sancho, Camacho-Vara de Rey, & Servera, 2017; Okumura et al., 2017; Schönenberg et al., 2017; Strehl et al., 2017; Sudnawa et al., 2018; van Doren et al., 2018; Zilverstand et al., 2017; Zuberer, Minder, Brandeis, & Drechsler, 2018). These effects sometimes even exceeded the ones obtained with pharmaceutical treatments in this context (e.g., *Ritalin*), making neurofeedback a serious and increasingly popular treatment alternative for children and adolescents with ADHD. Apart from ADHD and epilepsy, neurofeedback has been discussed as treatment for stroke (Kober, Schweiger, Reichert, Neuper, & Wood, 2017; Mottaz et al., 2015; Ros et al., 2017; T. Wang, Mantini, & Gillebert, 2017; Zich et al., 2017), addiction (D.-Y. Kim et al., 2015), depression and anxiety (R. W. Beck et al., 2017; Hammond, 2005; Kelley, Hortensius, Schutter, & Harmon-Jones, 2017; Mennella, Patron, & Palomba, 2017; Young, Misaki, et al., 2017; Young, Siegle, et al., 2017; Young et al., 2018), autism spectrum disorder (Coben, Linden, & Myers, 2010; Datko, Pineda, & Muller, 2018; Ramot et al., 2017), insomnia (Fovet et al., 2017; Schabus et al., 2017), Alzheimer's disease (Jiang, Abiri, & Zhao, 2017), obsessive compulsive disorder (Gonçalves, Batistuzzo, & Sato, 2017; Rance et al., 2018), Parkinson's disease (Philippens, Wubben, Vanwersch, Estevao, & Tass, 2017), schizophrenia (Orlov et al., 2018; Rieger et al., 2018), eating disorders (Sokunbi, 2018), post-traumatic stress disorder (Panisch & Hai, 2018), and many more (for an overview, see Tan et al., 2016).

Apart from its use in clinical contexts, neurofeedback is also increasingly popular in the training literature to enhance (cognitive) performance in healthy individuals. Attempts have been made to improve peak performance (e.g., of professional ath-

letes), attention, executive functioning, reaction times, orientation, psychomotor skills, memory, intelligence, mood, general well-being, or creativity (for a review, see Gruzelier, 2014a, 2014b). However, this wide variety of applications and the fact that neurofeedback is often used in practice by laypeople without appropriate training and background knowledge carries risks that should not be underestimated. Many researchers thus urge caution and criticize the careless use of neurofeedback as miracle cure for many disorders and cognitive problems (e.g., Hammond & Kirk, 2007). Furthermore, the placebo discussion is in full swing (Thibault, Lifshitz, & Raz, 2017b). Especially in the case of chronic tinnitus, many patients have undergone a variety of treatment attempts without success, and risks for unspecific placebo effects are thus rather high (see Chapter 3 for more details).

1.3 Open Issues and Purpose of this Dissertation

In this section, the aims of this thesis will be presented. As shown above, several theories already exist to explain the processes leading to chronic tinnitus, but no approach was able to fully explain this phenomenon. This has led to a variety of treatment options for individuals suffering from the constant phantom noise, most of which have been proven to be rather unspecific and experimental, and thus inefficient. Neurofeedback may be a valuable alternative in this context by providing an opportunity for tinnitus patients to re-adjust maladaptive plastic processes in their brains. To date, a handful of studies exists that aimed at implementing neurofeedback for this purpose. However, so far no attempts have been made to comprehensively summarize and critically discuss all these studies and its results. Therefore, this will be the first step in the thesis at hand.

Article I in chapter 2.1 is a comprehensive literature review in which electrophysiological findings and previous neurofeedback treatment attempts of tinnitus are summarized. The reviewing of literature clearly showed that mainly the use of frequency band training combined with the tinnitus-specific electrophysiological findings in the context of the TCD and SLIM model may be a highly promising approach to develop neurofeedback protocols for chronic tinnitus. However, in the review, also the poor methodological quality of many previous neurofeedback studies and the missing consensus in tinnitus research in general are addressed. In particular, many intervention trials worked with relatively small samples, poorly defined outcome measures that differed greatly between studies, and had no sufficient control over the study process.

To improve the field of neurofeedback treatment for chronic tinnitus, a larger

clinical project was planned, carefully taking into account the methodological considerations summarized in *Article I*. This neurofeedback training study was performed in cooperation with the Department of Otorhinolaryngology (University Hospital Zurich), and 53 chronic tinnitus patients were included to perform alpha/delta NFB training to alleviate symptoms. Outcome measures of this study have been a priori defined according to the recommendations of the European tinnitus research network, TINNET, and the study process has been standardized according to clinical and ethical guidelines. Apart from symptom measurements, also electrophysiological parameters have repeatedly been measured during the study to holt risks for unspecific placebo effects at an absolute minimum. Furthermore, to assess stability of changes, follow-up measurements have been performed up to 6 months after termination of the training phase. Data acquisition for this longitudinal intervention study lasted for approximately 2 years, and the amount of data obtained was immense due to the high number of subjects and the variety of tests and questionnaires (e.g., over 40 hours of EEG have been recorded, and nearly 1'500 questionnaires completed). The conducted project can thus be labeled the most comprehensive neurofeedback training study in tinnitus intervention to date.

Article II in chapter 2.2 summarizes data analysis of one of the two study groups. Working with a neurofeedback protocol previously used in other interventions (Crocetti, Forti, & Del Bo, 2011; Dohrmann, Elbert, Schlee, & Weisz, 2007; Dohrmann, Weisz, Schlee, Hartmann, & Elbert, 2007), this was a replication attempt. Results of data analysis confirmed the beneficial effects of neurofeedback on tinnitus symptoms. Both outcome measures, tinnitus-related distress as well as tinnitus loudness, were significantly reduced over the course of the training. Furthermore, the decrease of distress was stable as measured 3 and 6 months after the training period. Electrophysiological data showed that the trained alpha/delta ratio significantly increased due to the neurofeedback training, suggesting specific NFB training effects. In addition, control comparisons and correlation analyses have been performed to estimate unspecific effects of the training. In this context, it was shown that the increase of alpha/delta ratio was partially correlated with the decrease of tinnitus-related distress and that no effects in other (untrained) frequency bands occurred. However, topographical specificity of the training was not given as the trained ratio did not only increase over the four EEG electrodes used for measurement of feedback-relevant activity but also globally across the whole scalp. This speaks in favor of topographically wide-spread training effects and is explained with the rather poor spatial precision of traditional neurofeedback setups.

A second group of participants performed the same training but used more elec-

trodes and an implemented source estimation algorithm to focus the feedback on PAC activity specifically. The results of the comparison between the two groups are subject of *Article III* in chapter 2.3. Both groups showed reductions in tinnitus-related symptoms with no between-group differences according to the repeated-measures mixed model analysis of variance (ANOVA). Furthermore, electrophysiological training effects have been found for both groups on surface as well as on source level. In sum, the results suggested that NFB training following traditional feedback application on surface basis might lead to better effects on tinnitus. This issue is discussed in the context of newest findings about heterogeneous representation of distinct tinnitus subtypes in the brain which underlines the need for more individualized treatment procedures.

Chapter 2

Empirical part

2.1 Article I: Neurofeedback for Tinnitus Treatment – Review and Current Concepts.

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Abstract An effective treatment to completely alleviate chronic tinnitus symptoms has not yet been discovered. However, recent developments suggest that neurofeedback (NFB), a method already popular in the treatment of other psychological and neurological disorders, may provide a suitable alternative. NFB is a non-invasive method generally based on electrophysiological recordings and visualizing of certain

aspects of brain activity as positive or negative feedback that enables patients to voluntarily control their brain activity and thus triggers them to unlearn typical neural activity patterns related to tinnitus. The purpose of this review is to summarize and discuss previous findings of neurofeedback treatment studies in the field of chronic tinnitus. In doing so, also an overview about the underlying theories of tinnitus emergence is presented and results of resting-state EEG and MEG studies summarized and critically discussed. To date, neurofeedback as well as electrophysiological tinnitus studies lack general guidelines that are crucial to produce more comparable and consistent results. Even though neurofeedback has already shown promising results for chronic tinnitus treatment, further research is needed in order to develop more sophisticated protocols that are able to tackle the individual needs of tinnitus patients more specifically.

Keywords: Tinnitus, phantom perception, EEG, plasticity, heterogeneity, neurofeedback, frequency bands, alpha band

2.1.1 Introduction

Subjective tinnitus has been described as the constant perception of an auditory sensation that does not correlate to any external acoustic stimulus (Stouffer & Tyler, 1990). It can be perceived as either pitch or noise-like sound and its perception may be unilateral, bilateral or spread out in the whole head (De Ridder et al., 2014). In industrialized countries, roughly 10the population is affected by this stressful condition and many people suffer from sleeping or concentration problems, affected social interactions and psychological distress that can also lead to severe depression or anxiety impairments (Heller, 2003; Henry et al., 2005). The relatively large percentage of affected people, recently developed neuropsychological models, and the fact that, to date, no satisfactory potent treatment has been discovered may explain the increasing interest in tinnitus research. New findings on the pathophysiology of tinnitus have led to the development of several promising neuromodulatory techniques that have been shown to relieve symptoms of the chronic acoustic sensation and significantly increase quality of life for tinnitus sufferers (e.g., Eggermont & Roberts, 2004; Weisz, Dohrmann, & Elbert, 2007). One of them is neurofeedback, an already well-established form of neuropsychological treatment that recently enjoys great popularity due to its non-invasive nature, its long-lasting effects, its easy-handling and relatively low cost, as well as its rapid technological improvements. The purpose of this review is to summarize and discuss findings of neurofeedback studies for the treatment of chronic tinnitus. The focus is hereby laid on neurofeedback based on electrophysiological recordings with electroencephalography (EEG) or magnetoencephalography (MEG) but also a short summary of new innovative methods (e.g., real-time functional Magnetic Resonance Imaging, rt-fMRI) will be given. In a first step, an overview about popular models of tinnitus genesis will be provided, and studies investigating chronic tinnitus with EEG or MEG will be presented and critically discussed. Next, the development and history of neurofeedback will be briefly introduced and the different neurofeedback protocols used in tinnitus treatment summarized and evaluated. Finally, limitations of existing treatment studies will be discussed, and implications for future studies will be given.

2.1.2 Tinnitus Models and Electrophysiological Studies

Tinnitus was first assumed to be solely generated in the ear or by a dysfunction of the auditory nerve (Eggermont, 1990; Møller, 1984), but the focus of attention quickly shifted to the human brain after (P. J. Jastreboff, 1990) proposed what is nowadays known as the *neurophysiological model of tinnitus*. Even though some form of inner ear damage indeed seems to be a necessary prerequisite, (P. J. Jas-

treboff, 1990) suggested central processes in the auditory cortex, the limbic system, and prefrontal areas to be crucial for tinnitus genesis. Later models picked up this idea and tried to specify the neuroplastic alterations emerging after auditory deafferentation. In this context, an increase in central gain in subcortical structures of the auditory pathway (Noreña, 2011), reorganization of tonotopic maps in the primary auditory cortex (Mühlnickel et al., 1998), a thalamocortical dysrhythmia (Llinás et al., 1998; Llinás et al., 1999; Llinás et al., 2005; Weisz, Dohrmann, & Elbert, 2007) and changes in neural synchrony (Eggermont & Roberts, 2004; Noreña & Eggermont, 2003; Seki & Eggermont, 2003; Weisz, Moratti, et al., 2005), or a failing top-down noise-canceling mechanism (Rauschecker et al., 2010; Rauschecker et al., 2015) have been discussed. Furthermore, global workspace models emphasize the importance of networks beyond the auditory system (De Ridder et al., 2014), and frameworks of filling-in missing auditory information have been suggested in a Bayesian way (De Ridder, Elgoyhen, et al., 2011; De Ridder et al., 2006; De Ridder & Vanneste, 2014) or based on predictive coding (Sedley et al., 2016).

2.1.2.1 First Wave of Electrophysiological Studies

Apart from animal experiments, brain imaging and morphometry studies, the investigation of resting-state brain activity with electrophysiological methods, such as EEG or MEG, enjoys great popularity in tinnitus research (Adjamian, 2014). In order to pinpoint neural correlates of the ongoing tinnitus sensation, first studies compared spontaneous brain activity of tinnitus patients at rest with the one of healthy controls. In this context, most investigations focused on the analysis of neuronal oscillations separated into distinct frequency bands: delta (0.5–4 Hz), theta (4.5–8 Hz), alpha (8.5–12 Hz), beta (12.5–35 Hz), and gamma (35.5–80 Hz). Following this approach, early studies (Ashton et al., 2007; Kahlbrock & Weisz, 2008; Lorenz, Müller, Schlee, Hartmann, & Weisz, 2009; Weisz, Moratti, et al., 2005; Weisz, Müller, et al., 2007) found a relatively consistent pattern of enhanced activity in delta- and gamma frequencies, alongside with reduced amounts of alpha oscillations over temporal areas of tinnitus patients (for a review, see Adjamian, Sereda, & Hall, 2009; Schlee et al., 2008). These findings have been interpreted in the framework of the *thalamocortical dysrhythmia model* (TCD), originally proposed by (Llinás et al., 1998; Llinás et al., 1999; Llinás et al., 2005) and later significantly refined by Weisz, Dohrmann, and Elbert (2007) to the *synchronization by loss of inhibition modulation* (SLIM) model. Both models aim at sketching tinnitus genesis as the result of an imbalance between inhibition and excitation in thalamocortical circuits. Loss of sensory input (deafferentation) gives raise to low frequent self-oscillations of thalamic cells which activate the auditory cortex and can thus be

measured as oscillations in a slow delta rhythm on the scalp. At the same time, input deprivation also leads to a downregulation of inhibitory mechanisms which is reflected in alpha desynchronization in the resting-state EEG or MEG. This decrease of inhibition is then proposed to lead to spontaneous synchronization of firing reflected in increasing activity in fast gamma oscillations. This pattern of increased resting-state delta and gamma and decreased alpha has thus been termed the *neural signature of tinnitus*, and gamma has been interpreted as the neuronal substrate of the sound percept itself.

2.1.2.2 Limitations of the Early Studies

One of the major flaws of these early studies, however, was that they did not consider that chronic tinnitus is a very heterogeneous phenomenon and can differ substantially between individuals. It has clearly been shown that the subjective experience of the chronic sound (intensity, pitch, location) as well as the related distress and comorbid symptoms vary considerably among sufferers (Landgrebe et al., 2010; Langguth et al., 2013; van den Berge et al., 2017; Weidt et al., 2016). In addition, the underlying neuroanatomical and neurophysiological alterations may be far from homogenous in the population of tinnitus patients. Instead of comparing tinnitus patients with healthy controls, more recent studies thus focused on differences *within* the tinnitus sample with the ultimate goal of identifying distinct subtypes of tinnitus and finding different forms of treatment for each of these subtypes.

Another issue that the earlier studies had to deal with is the fact that electrophysiological methods suffer from rather poor spatial resolution. In terms of neuroscience, the *inverse problem* describes the fact that signal as measured by electrodes or magnetometers on the scalp could be generated by infinite combinations of neuronal sources (Scherg & Berg, 1991). The described pattern of tinnitus-specific oscillations found in the earlier studies, even though measured over temporal areas, could therefore have been generated in (or significantly altered by) cell assemblies outside of the primary auditory cortex. Different *source estimation algorithms* have been developed in the recent past to solve this inverse problem as well as possible by applying different *a priori* assumptions. With these algorithms the source of a measured signal can be estimated and spatial resolution of resting-state EEG and MEG measurements significantly increased (Michel et al., 2004). Standardized Low Resolution Electromagnetic Tomography (sLORETA) (Pascual-Marqui, 2002) or beamformer algorithms (Grosse-Wentrup, Liefhold, Gramann, & Buss, 2009; Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005; van Veen, van Drongelen, Yuchtman, & Suzuki, 1997) are examples of fairly precise and therefore relatively popular source

estimation techniques.

The new focus on differences within the tinnitus population and the improvements in electrophysiological analysis methods have led to a veritable boom of resting-state tinnitus studies. Some investigations have confirmed the neuronal tinnitus code and auditory gamma as its major brain correlate by applying sLORETA (Moazami-Goudarzi, Michels, Weisz, & Jeanmonod, 2010; van der Loo et al., 2009; Vanneste, van de Heyning, & De Ridder, 2011a) or beamformer (Ortmann et al., 2011) source estimations to the measured signal, reporting correlations between tinnitus loudness and auditory gamma (van der Loo et al., 2009) or by performing intervention studies with acoustic coordinated reset (Adamchic, Langguth, et al., 2014; Adamchic, Toth, Hauptmann, & Tass, 2014; Adamchic et al., 2017; Tass et al., 2012). Schlee et al. (2014), on the other hand, found decreased power (and variability) only for the lower (8–10 Hz) but not for the upper alpha band (10–12 Hz) and other studies failed completely to find the expected pattern in the auditory areas (Meyer, Luethi, Neff, Langer, & Büchi, 2014; Song, Punte, et al., 2013; Vanneste, Joos, & De Ridder, 2012; Vanneste, van de Heyning, & De Ridder, 2011b; Zobay & Adjamian, 2015). Furthermore, two studies (Sedley & Cunningham, 2013; Sedley et al., 2012) discussed the possibility that auditory gamma oscillations could emerge as an attempt of the brain to suppress the tinnitus percept rather than causing it.

2.1.2.3 Tinnitus Network(s) and Areas Beyond the Auditory Cortex

In neuroscience, the gamma frequency range has also been debated as a binding medium connecting activity of various circuits to form a unified percept (Singer, 1993). Already Schlee et al. (2009) reported gamma-related abnormalities in a network with core regions in prefrontal, orbitofrontal, and parieto-occipital areas. Later the different parallel networks that may differentially contribute to the various tinnitus symptoms were described in more detail (De Ridder, Elgoyhen, et al., 2011; De Ridder et al., 2014; Vanneste & De Ridder, 2012a). A *tinnitus core network* was proposed to generate the sound *per se* and code its intensity and location (holocranial, uni- or bilateral). Other networks were introduced as modulating the sound type (sine wave tone, hissing, ringing) as well as aversive states and feelings (e.g., distress or mood) of tinnitus (De Ridder et al., 2014). An increased and persisting amount of gamma oscillations and coupling with slow-waves could thus suggest that activity of these widely-distributed brain networks is constantly *bound together* (synchronized), and a unified tinnitus percept is formed with its very own characteristics for each individual coded in the relevant sub-networks. In order to capture the tinnitus phenomenon in its entirety, areas outside of the central auditory regions therefore have

to be considered. Furthermore, the specificity of the measured EEG-patterns has to be carefully validated as related disorders might produce similar findings (e.g., Joos, Vanneste, & De Ridder, 2012; Meyer et al., 2017). These considerations are also relevant with regard to the development of neurofeedback protocols.

Apart from investigations comparing brain networks of tinnitus patients and healthy controls based on analyses with graph theory or machine learning algorithms (Mohan, De Ridder, & Vanneste, 2016a, 2016b, 2017; Mohan, Moreno, Song, De Ridder, & Vanneste, 2017), a multitude of recent electrophysiological studies attempt to find specific correlates in neural networks for the different aspects of tinnitus (Adjamian, 2014; De Ridder, Vanneste, Langguth, & Llinás, 2015; Eggermont, 2015; Elgoyhen et al., 2015). These studies mainly investigated tinnitus-related distress or loudness, but also covered tinnitus type, pitch, location/laterality, duration, age of onset, day-time awareness, or related problems such as hearing loss, hyperacusis, depression, or general quality of life (a detailed summary is provided in Table 2 in Appendix A). The most consistent findings are reported for tinnitus-related distress, which seems to be represented in a network ranging from structures of the limbic system (e.g., anterior cingulate cortex and amygdala) to prefrontal areas (e.g., dorsolateral prefrontal cortex), and also includes the insula. Altogether, however, the results of these studies are rather heterogeneous, and attempts of replication are scarce and partly fail to confirm previous findings (Meyer et al., 2017; Pierzycki et al., 2015). This can partially be explained by different EEG or MEG hardware used for resting-state recordings, different paradigms during the measurement [e.g., length of measurement, operationalization of tinnitus symptoms, or condition of resting-state (eyes open/closed) used for the analysis], different source estimation algorithms and data analysis procedures. To resolve this issue, scholars of the European research network TINNET[1] are channeling their efforts to establishing general guidelines for (electrophysiological) tinnitus studies and collecting comparable data in a large database[2]. In order to tackle the problem of tinnitus heterogeneity, it is thus of utmost importance that future studies take these guidelines into consideration, report also null or conflicting results and further also extend their focus to replicating previous findings.

2.1.3 Neurofeedback

Applying neurophysiological methods, neurofeedback is a noninvasive neuromodulation technique which records a subject's neuronal activity, extracts relevant aspects

[1] http://tinnet.tinnitusresearch.net/
[2] https://www.tinnitus-database.de/

of brain processes by means of real time signal processing and returns feedback to the subject as visual or auditory stimuli. The aim of neurofeedback is to change behavioral traits or medical conditions associated with altered neural activity as demonstrated for chronic tinnitus in the previous section. This is generally done by means of operant conditioning (i.e., rewarding of wanted, inhibiting of unwanted changes) whereby the subjects learn to voluntarily change their own brain activity in the desired direction.

2.1.3.1 A Brief History of Neurofeedback

In the early 1930's and 1940's, human studies already suggested the capability of the central nervous system to alter neural activity patterns by means of conditioning methods (Jasper & Shagass, 1941; Loomis, Harvey, & Hobart, 1936). Later, Wyrwicka and Sterman (1968) were able to train cats to change their brain activity in a specific direction, and, shortly after that, the first study with human subjects in this context was published (Sterman & Friar, 1972). In the following years, neurofeedback was intensively tested and showed promising results mainly in treatment studies with epilepsy and attention deficit hyperactivity disorder (ADHD) (J. O. Lubar & Lubar, 1984; J. F. Lubar & Bahler, 1976). For ADHD, neurofeedback already found acceptance as alternative to established medication based treatment, due to its non-invasive character, the almost complete absence of any side-effects and high self-efficacy experienced by the subjects (Arns, De Ridder, Strehl, Breteler, & Coenen, 2009; Gevensleben et al., 2009; Lévesque, Beauregard, & Mensour, 2006; J. F. Lubar et al., 1995; Strehl et al., 2017). Apart from that, effectiveness and feasibility of neurofeedback are more and more investigated in the context of many other psychological disorders and neurological conditions ranging from the treatment of depression (Kelley et al., 2017), anxiety (Mennella et al., 2017), or autism (Datko et al., 2018) to stroke patients (Kober et al., 2017) and prevention of Alzheimer's disease (Jiang et al., 2017). Today, quality control is an important aspect in the neurofeedback field. The Biofeedback Certification International Alliance (BCIA)[3] certifies bio- and neurofeedback practitioners who meet certain requirements and the Association for Applied Psychophysiology and Biofeedback (AAPB)[4] recently released the 3rd edition of *Evidence-Based Practice in Biofeedback and Neurofeedback*, a document that summarizes treatment efficacy for various disorders (Tan et al., 2016).

[3] http://www.bcia.org
[4] https://www.aapb.org

2.1.3.2 Common Neurofeedback Paradigms

Neurofeedback training of classical definitions of distinct frequency bands (i.e., delta, theta, alpha, beta, and gamma) are the most commonly used protocols in the current literature. The main field of frequency band neurofeedback is the treatment of ADHD, where often a combination of different frequencies is trained (Lofthouse et al., 2012). However, classic frequency band training has also been adapted for other disorders, most prominently anxiety or affective problems (Hammond, 2005). Importantly, neurofeedback training based on this paradigm ultimately depends on findings of fundamental research about disorder-specific neural alterations and can even be used to confirm or disprove these findings.

Sensorimotor rhythms (SMR) are defined as EEG oscillations in the lower beta range (12 – 20 Hz). They are generally measured over the sensorimotor cortex and proposed to originate from the ventrobasal nucleus in the thalamus (Howe & Sterman, 1972, 1973). Neurofeedback training based on SMR mainly found application in the treatment of epilepsy (Sterman & Egner, 2006) or ADHD (T. Fuchs et al., 2003; Monastra et al., 2002). Slow cortical potentials (SCP's) describe very slow oscillations in a range of 0.3–1.5 Hz. They describe slow, discrete, and continuous shifts (up to seconds) of the overall cortical distribution of electrical activity representing increased or decreased excitability of underlying neuronal structures. SCP's are usually recorded with a single electrode in a central position (Cz) and are proposed to reflect cognitive or motor preparation (Hammond, 2011). Initially, SCP training was exclusively applied in trials with patients suffering from epilepsy (Rockstroh et al., 1993) but later also found application in the treatment of ADHD (Strehl et al., 2017).

Infra-low neurofeedback (ILN) relies on training of even slower brain oscillations, ranging from 0.001 to 1.5Hz (Vanhatalo et al., 2004). Infra-low oscillations were shown to correlate with other frequency bands as well (Monastra et al., 2002). There is an overlap with SCP-based neurofeedback, which mainly differs in the recording of SCP's with a single central electrode and thus a training of a more summarized potential over the whole head. Positive effects of ILN on different neurological conditions were reported in case reports (Legarda et al., 2011). In z-score neurofeedback, the training protocol for an individual patient is based on previous recordings of EEG data and comparison to a healthy age-matched normative database (Thatcher, 2010). During the neurofeedback training, patients try to normalize their EEG patterns and minimize deviations from this control group. This NFB alternative is a rather data-driven technique, and some studies report successful

treatment of various disorders (e.g., schizophrenia, addiction, ADHD, or personality, anxiety, and affective disorders) with z-score neurofeedback (Simkin, Thatcher, & Lubar, 2014; Surmeli & Ertem, 2009; Surmeli, Ertem, Eralp, & Kos, 2012).

Functional magnetic resonance imaging (fMRI) was introduced to the field of neurofeedback to obtain a better spatial resolution. Real-time acquisition of blood oxygenation level dependent (BOLD) signals demonstrates increased neural activity according to higher oxygen supply to active neurons (Ogawa, Lee, Kay, & Tank, 1990). Although newer to the field, a large quantity of clinical treatment studies already focused on the use of real-time fMRI neurofeedback (Sulzer et al., 2013). The higher spatial resolution of fMRI neurofeedback, however, does not come without limitations. Increased blood oxygenation can be measured only after a delay of several seconds and is an indirect correlate of underlying neuronal processes. Compared to electrophysiological methods, the temporal resolution of fMRI is thus rather poor, and fast fluctuations cannot be captured accordingly and used for the feedback. Additionally, it is questionable if an MRI-scanner is a favorable setting to perform neurofeedback because of the limited space and the loud constant background noise. For tinnitus patients, this is a huge drawback, in particular in those individuals suffering from additional hyperacusis.

To address the poor spatial resolution of single- or multi-electrode EEG and MEG recordings, neurofeedback techniques have also been combined with source estimation algorithms. Congedo, Lubar, and Joffe (2004) introduced the first tomographic neurofeedback protocol based on the inverse solution technique LORETA (Pascual-Marqui, Michel, & Lehmann, 1994). This approach has subsequently been intensely tested mainly in the context of ADHD treatment (Cannon et al., 2014; Cannon, Congedo, Lubar, & Hutchens, 2009; Cannon et al., 2007; Cannon et al., 2006; Koberda, Koberda, Bienkiewicz, Moses, & Koberda, 2013; Koberda, Moses, Koberda, & Koberda, 2012) and has recently been further refined (Bauer & Pllana, 2014; Congedo, 2006; Kopřivová et al., 2013; Pllana & Bauer, 2011; White, Congedo, & Ciorciari, 2014).

2.1.3.3 Neurofeedback and Tinnitus: Existing Studies

Presently, only a handful of studies investigated the efficacy of neurofeedback in the treatment of chronic tinnitus according to standard searching tools such as *PubMed*[5]. An overview is provided in Table 1.

[5]https://www.ncbi.nlm.nih.gov/pubmed/

Table 1: Summary of studies investigating neurofeedback for treatment of tinnitus

Authors	N	Protocol	Electrodes/ Sources	Feedback	Behavioral findings	Neuronal findings
Crocetti et al. (2011)	15	$\alpha\uparrow$ $\delta\downarrow$ 12 sessions	F3, F4, Fc1, Fc2	Plane moving up and down (with audio-visual reinforcement)	Distress ↓ Loudness ↓	α/δ-ratio ↑ (not all participants were able to manipulate α & δ successfully)
Dohrmann et al. (2007a,b)	Group 1: 11 Group 2: 5 Group 3: 5 Controls: 27	Group 1: $\alpha\uparrow$ $\delta\downarrow$ Group 2: $\alpha\uparrow$ Group 3: $\delta\downarrow$ Control: FDT 10 sessions	F3, F4, Fc1, Fc2	Fish moving up and down	All groups: Distress ↓ Loudness↓ Group 1: strongest relief Controls: no reduction	All groups: $\alpha\uparrow$ & $\delta\downarrow$ Correlation with decrease in loudness
Gosepath et al. (2001)	NFB-Group: 40 Controls: 15	$\alpha\uparrow$ $\beta\downarrow$ 15 session	P4	Auditory and visual (not further explained)	Distress ↓	Group 1 (n=24): $\alpha\uparrow$ Group 2 (n=16): $\beta\downarrow$ Controls: no effect
Hartmann et al. (2013)	NFB-Group: 8 Controls: 9	$\alpha\uparrow$ 10 sessions Controls: rTMS	Source space projection on two temporal sources	Smiley	Distress ↓ Controls: no reductions	$\alpha\uparrow$ estimated over r PAC
Schenk et al. (2005)	Group 1: 23 Group 2: 13	Group 1: $\alpha\uparrow$ Group 2: $\beta\downarrow$ Group 3: $\alpha\uparrow$ $\beta\downarrow$	Group 1: P4 Group 2: C3	Floating ball and melody	Distress ↓	Both groups: $\alpha\uparrow$
Vanneste et al. (2016)	Group 1: 23 Controls 1: 17 Controls 2: 22	Group 1: $\alpha\uparrow$ $\beta\downarrow$ $\gamma\downarrow$ Controls 1: $\alpha\uparrow$ $\beta\downarrow$ $\gamma\downarrow$ Controls 2: passive 15 sessions	sLORETA Group 1: PCC Controls 1: LG	Green bar moving up and down	Group 1: distress ↓ Controls: no reduction	No alterations in target areas for α, β and γ Changes in functional and effectivity connectivity
Weiler et al. (2002)	1	$\alpha\uparrow$ $\beta\uparrow$ $\delta\uparrow$ $\theta\uparrow$	19 electrodes	Varying	Depression ↓ Anxiety ↓ Tinnitus ↓	No analysis

Note. ↑, increase; ↓, decrease; r PAC, right primary auditory cortex; PCC, posterior cingulate cortex; LG, lingual gyrus.

In the first study in this context published by (Gosepath, Nafe, Ziegler, & Mann, 2001), 40 patients suffering from chronic tinnitus and 15 control subjects underwent neurofeedback training. The training protocol included alpha training (8–13 Hz) alongside with a reduction of beta oscillations (14–30 Hz). While one group of patients (n = 24) was able to only increase their alpha activity, the effects of the other group (n = 16) were limited to the decrease of beta oscillations. All patients, however, reported to be less disturbed by their tinnitus after the training, indicated by significant decrements in scores of the tinnitus questionnaire (TQ) (Goebel & Hiller, 1994). Control subjects underwent identical training but without real-time feedback and did thus not show any changes in alpha or beta activity. Schenk, Lamm, Gündel, and Ladwig (2005) aimed at replicating the findings from (Gosepath et al., 2001) with the aforementioned protocol. Before assigning them to different study groups, participants underwent baseline EEG-recordings at rest and during a stress test. Participants (n = 40) were assigned to three different groups according to their results. Twenty-three subjects showing decreased alpha activity under stress were allocated to a first group and set to train alpha activity (8–13 Hz) in the subsequent neurofeedback training. The second group consisted of 13 patients with increased beta activity in the stress condition and their treatment protocol thus aimed at the decreasing of beta oscillations (14–30 Hz). Four patients could not be assigned to either of the aforementioned groups according to their spontaneous brain activity and hence were allocated in a third group that had to increase alpha and decrease beta activity simultaneously. Subjects of the first group were able to increase their alpha activity, whereas subjects of the second group failed to significantly decrease their amount of beta oscillations. Surprisingly, also subjects of the second group showed increases in alpha activity even though it was not intended with the feedback. Reduced subjective tinnitus distress in terms of a reduction of TQ scores was reported for both groups. The third group was excluded from data analysis due to its small size.

A third rather explorative study shall briefly be mentioned. In a case report, Weiler, Brill, Tachiki, and Schneider (2002) used z-score neurofeedback for one patient with bilateral tinnitus. The feedback protocol was based on EEG recordings prior to the training where decreased delta, theta, alpha and beta activities compared to 20 control subjects had been observed. The results indicated a normalization of depressive and anxiety symptoms and the patient reported that tinnitus was only occasionally present. However, no comparisons of pre–post changes in EEG patterns have been drawn in this study.

Even though these three first attempts to treat tinnitus with neurofeedback

seemed to be promising, they should not be over-interpreted. First, the training-protocols were chosen rather arbitrarily and not based on previous findings of tinnitus-specific neural abnormalities. Moreover, the fact that patients of all groups reported significant improvements in tinnitus-related distress, regardless of their actual alterations of neural activity, speaks in favor of unspecific effects of the neurofeedback training. Especially the unintended increase of alpha activity in the second group of the study by Schenk et al. (2005) suggests that a general relaxation effect might have had a bigger impact than the actual neurofeedback protocol. In general, these first three studies rather aimed at helping their patients relax and reduce their general level of stress, and it is thus not surprising that reduced distress was reported after the training. However, since knowledge about the origins of tinnitus was still rare at this time, these studies can clearly be seen as pioneering works in the treatment of tinnitus with neurofeedback.

The TCD-model (Llinás et al., 1999; Llinás et al., 2005) and the proposition of the *neural signature of tinnitus* (Weisz, Dohrmann, & Elbert, 2007) gave rise to new and potentially more appropriate neurofeedback protocols. Dohrmann, Elbert, et al. (2007), Dohrmann, Weisz, et al. (2007) developed their neurofeedback protocols by reference to these findings and aimed at an increasing of alpha and a decreasing of delta activity. Twenty-one patients suffering from chronic tinnitus were included into their study and further assigned to three different treatment groups (see Table 1). For the neurofeedback application 4 fronto-central electrodes (F3, F4, Fc1, and Fc2) were chosen because the recorded signal is most likely generated in the auditory cortex according to the authors. For a forth group of tinnitus patients (n = 27) frequency discrimination training (FDT) was applied aiming at a change of hearing-loss induced cortical map reorganization. Data analysis showed a significantly increased ratio between alpha and delta activity for the three neurofeedback groups suggesting an increase of alpha alongside with a decrease of delta over temporal auditory regions. These alterations were also correlated with a significant decline of tinnitus loudness for tinnitus patients. Subjects who were able to modify both bands simultaneously in the desired way showed the strongest relief from tinnitus compared to other groups (i.e., subgroups of patients with only alpha-, only delta-, or no change). Furthermore, the training generally resulted in a reduction of tinnitus related distress that was still notable even 6 months after the termination of the training. No statistically meaningful effects regarding tinnitus loudness or distress were found in the FDT group. In order to replicate these findings, Crocetti et al. (2011) conducted a study with 15 normal hearing tinnitus patients and tried to train them in decreasing delta and increasing alpha frequency bands. Even though no significant differences between pre- and post-training EEG patterns have been

found, the results suggested an obvious trend toward an increasing alpha/delta ratio. In addition, scores evaluated with the Tinnitus Handicap Questionnaire (THI) (Newman, Jacobson, & Spitzer, 1996) indicated significant improvements, which were maintained after the end of the training period.

All in all, these two studies suggested the protocol of upregulating alpha and downregulating delta to be a highly promising approach in tinnitus treatment. However, the surface-based nature of the neurofeedback application by simply using four electrodes on the scalp could not ensure that the brain activity used for the feedback indeed originated in the auditory areas. To address this problem, Hartmann, Lorenz, Müller, Langguth, and Weisz (2013) used a 32-channel EEG system and projected the recorded activity on the surface to eight regional dipole-sources, of which two were situated in the temporal cortex. Eight subjects of this investigation received neurofeedback treatment to train an increase of alpha power and nine subjects were treated with repetitive transcranial magnetic stimulation (rTMS). With the completion of the training, only patients of the neurofeedback group showed improved tinnitus distress scores. In comparison to the control group with rTMS treatment, they achieved significantly ameliorated scores in the TQ. Additionally, a comparison of MEG resting-state activity before and after treatment combined with spatial filtering based on a LCMV beamformer algorithm (van Veen et al., 1997) revealed a significant increase of alpha activity over the right primary auditory cortex. According to Hartmann et al. (2013) this proves that alpha activity can be systematically altered in the primary auditory cortex which helps restore the disturbed excitatory–inhibitory balance of tinnitus patients.

Finally, two recently published neurofeedback studies shall be mentioned. Milner et al. (2015) used SCP neurofeedback training in a case report and could show decreased tinnitus pitch and loudness as well as a reduction of delta and theta frequencies over left hemispheric fronto-temporal and temporo-occipital electrodes which they interpret as a normalization of tinnitus-specific activity. Vanneste, Joos, Ost, and De Ridder (2016) applied neurofeedback combined with sLORETA source estimation to a group of 58 tinnitus patients. A first group (n = 23) of this study received alpha-up training, and beta- and gamma-down training whereby the feedback was limited on the activity that was estimated to originate over the posterior cingulate cortex (PCC). A second group of 17 tinnitus patients received the same training but for activity over the lingual gyrus and a third group (n = 18) did not receive any treatment at all. Decreased tinnitus distress was only found for the PCC-group but no significant changes in any frequency bands were found in the trained areas. However, decreased cross-frequency coupling (i.e., alpha to beta and

alpha to gamma power nesting) in the PCC and changes in functional and effective connectivity between PCC and different areas of the distress network suggest a specific effect of this training.

Finally, even though this review mainly focuses on neurofeedback based on electrophysiological recordings, it shall be noted that also real-time fMRI protocols are currently being developed and tested for tinnitus treatment with promising results (Emmert et al., 2017; Haller, Birbaumer, & Veit, 2010; Haller et al., 2013). In their investigations, the auditory cortex of tinnitus patients is first precisely localized thanks to the good spatial resolution of fMRI, and, subsequently, neurofeedback training aiming at reducing auditory BOLD activity provided. Even though this protocol leads to the intended neuronal alterations, no significant effects on tinnitus symptoms have been reported (Emmert et al., 2017).

2.1.3.4 Limitations of Neurofeedback Training Studies

Currently, the AAPB rates the efficacy of chronic tinnitus treatment with neurofeedback as *possibly efficacious* (level 2) (Tan et al., 2016). Although various neurofeedback training protocols showed promising results in treatment of several neurological disorders, there still remain limitations and open issues which need to be addressed. In particular, EEG- and MEG-based neurofeedback studies are often criticized about the low spatial resolution of electrophysiological recordings. Despite more refined source estimation algorithms, an uncertainty about the precision of the estimation remains, which is especially important when changes in frequency bands are considered as primary outcome measures. Studies that are able to verify specific effects in the brain areas of interest are still scarce and successful improvements of certain symptoms are thus often criticized to be the mere result of unspecific placebo effects (Thibault, Lifshitz, & Raz, 2016, 2017b). Expectations of researcher and participant, the treatment condition in general (e.g., taking time off from a busy work schedule) and interactions with the practitioner (such as, the simple meeting with a clinician) can contribute greatly to the improvement of psychological symptoms. This problem is especially predominant in the context of chronic tinnitus therapy where most participants turn to neurofeedback hopefully after repeatedly being told by their doctors that nothing can be done to treat tinnitus and having undergone a wide variety of (sometimes rather questionable) treatments on their own.

One way to resolve this issue is to improve study designs and conduct double-blind trials with control groups using a form of sham neurofeedback. In this context, Thibault et al. (2016) suggest the use of prerecorded feedback of other participants,

feedback of another disease-unrelated brain area, or inverse feedback protocols that reward unwanted and inhibit wanted changes of brain activity. The use of sham-control is, however, difficult to establish in clinical neurofeedback trials because of several reasons. First, participation in neurofeedback treatment studies requires considerable investments in time and energy on the part of participants as they generally have to attend multiple training sessions over the course of several weeks. Furthermore, in sham-controlled clinical studies, participants always enter a trial with some form of expectation and hope to be part of the treatment group. Absent success after the first training sessions may lead to a misleading belief that they instead have been assigned to the control group which negatively affects their motivation and further success in the training process (Strehl et al., 2017). These drawbacks of placebo-controlled trials have to be considered and alleviated with appropriate designs, such as a cross-over approach where one group of participants receives sham training first while the other starts with verum treatment. In a second step the protocols are swapped so that both groups undergo sham- as well as verum-neurofeedback. In this context several authors point to the importance of a systematic investigation of non-specific factors in neurofeedback studies (Friedrich, Wood, Scherer, & Neuper, 2014; Sitaram et al., 2017; Thibault et al., 2017b). Appropriate knowledge about the factors favoring and the ones hindering success in neurofeedback treatment can indeed lead to a better understanding of the actual mode of action of neurofeedback as well as help improve the treatment setting in order to optimize therapy outcomes for patients.

A major flaw of previous neurofeedback studies is that most of them settle for reporting positive effects of their trained protocol. It is known, however, that there is a wide variability among the efficacy of neurofeedback treatment for different subjects. While some are able to successfully self-regulate their neural activity in the desired way and show improvements of corresponding symptoms (responders), others fail to do so (non-responders) (Friedrich et al., 2014). This issue was described as *neurofeedback inefficacy* by Alkoby, Abu-Rmileh, Shriki, and Todder (2017) who provide a thorough review about this currently existing topic. In their publication, they chose 20 papers published after 2010 at random and found that only two of them reported the actual number of responders and non-responders in their studies. This, of course, hampers a proper evaluation of the feasibility of a given neurofeedback protocol for the treatment of a certain disorder. For one thing, positive effects of the training might be concealed or confounded by the negative results of non-responders in the clinical trial. Furthermore, information provided about responder and non-responder groups helps define and analyze factors for success or failure of the protocol. That is, by means of a thorough investigation of the attributes of

responders and non-responders, predictors for (un-) successful neurofeedback can be identified, which can be used to improve training protocols for future patients.

Another issue in this context is the high heterogeneity among outcome measures and definitions to appropriately measure success or failure used in previous neurofeedback studies. On the one hand, it can be useful to use a wide variety of outcome measures in a clinical study in order to account for changes which might not be anticipated in the first place. For instance, it can be important to measure the general level of stress of tinnitus patients as the positive effects of neurofeedback could also be explained by a decrease of the general stress condition of the patient. However, guidelines need to be established which suggest the use of certain questionnaires or tests for a given field of interest to which scholars can relate when planning an investigation (substantial work in the tinnitus field is currently being done by Hall et al. (2016) in this context). This will limit the amount of different outcome measures in clinical trials, promote the use of well-established and validated questionnaires, and foster direct comparability between findings of different investigations. Additionally, guidelines in the context of neurofeedback treatment need to answer the question as to what can be regarded as successful or unsuccessful training and how to distinguish responders from non-responders. Is it already sufficient that a given symptom simply changes over the course of a training in a positive way or does it have to improve by a certain amount (e.g., an increase by certain points in a questionnaire score)? What, on the other hand, needs to happen to and in between brain circuits? How and how much does neural activity have to be altered by the neurofeedback treatment so that an individual can be labeled as a responder? Even though some publications already tried to postulate criteria or guidelines (Enriquez-Geppert, Huster, & Herrmann, 2017; Gruzelier, 2014c; Rogala et al., 2016), many open issues remain in this regard.

2.1.4 Conclusion

In this review, we summarized and discussed the current state of electrophysiological brain research in the field of chronic tinnitus as well as recent advances of neurofeedback treatment. Up to date, only a handful of studies exist that investigated feasibility of neurofeedback protocols for chronic tinnitus patients. While the first studies in this context rather focused on creating a general state of relaxation for the subject, later trials considered tinnitus-specific alterations in brain activity based on comparisons of EEG or MEG resting-state recordings between tinnitus patients and healthy controls. The main region of interest in these studies was the

auditory cortex, and fairly good results have been achieved following this approach. With the newer developments in tinnitus research and the numerous investigations dealing with differences within the tinnitus population, which take into account the substantial amount of heterogeneity amongst tinnitus sufferers, also other potential tinnitus-related brain areas can be targeted in future neurofeedback studies. A good example in this regard is the recent publication by Vanneste, Joos, Ost, and De Ridder (2016) where the posterior cingulate cortex as part of the tinnitus distress network has been targeted. Furthermore, this investigation is the only neurofeedback study in the context of chronic tinnitus treatment to date that included a control group with training of a tinnitus-irrelevant brain area in its design.

To sum up, even though often criticized in the recent past, results of current studies suggest that neurofeedback seems to be a promising method for efficient tinnitus treatment and may enjoy great popularity in the future. The ultimate goal may be to develop different neurofeedback alternatives for a given subgroup of tinnitus sufferers or even establish neurofeedback on an individualized basis for each patient. In this context, multi-location and multi-frequency neurofeedback protocols with adequate source estimation algorithms, which are able to train multiple brain networks in power and maybe even connectivity changes simultaneously, can be seen as the gold standard for future neurofeedback protocols. At the moment, however, there still exist several challenges that need to be overcome. A general issue are technological aspects of electrophysiological measurements (e.g., the limited spatial precision of resting-state EEG recordings) and neurofeedback applications (e.g., the implementation of connectivity-based neurofeedback protocols) that need to be improved. Regarding the treatment of chronic tinnitus in particular, results of existing fundamental studies are still too heterogeneous in order to suffice for the development of more sophisticated neurofeedback protocols. One possibility to resolve this latter issue is by means of the establishment of general guidelines about adequate symptom assessment, measurement paradigms, and analysis methods. In this way, more coherent and comparable results should be published in order to lead to a better understanding of tinnitus heterogeneity and its underlying alterations in brain networks that could be tackled by future neurofeedback protocols. Additionally, this urgent need for guidelines has been shown to be an open issue in the field of clinical neurofeedback research in general. Clarity is needed about how to separate responders from non-responders, and which outcome domains and measurements are best suited to do so. Furthermore, also non-specific effects of the training have to be taken into account and systematic investigations about the most (or least) favorable neurofeedback settings and treatment conditions are needed.

2.1.5 Appendix A

Table 2: Summary of recent electrophysiological studies investigating chronic tinnitus

Reference	Study Design	Source Estimation, Connectivity	Feature (Measurement)	Analysis	Findings
Adamchic, Langguth, et al. (2014)	Intervention (ACR)	BESA (source montage) Phase-amplitude CFC	Pitch	Responders with pitch change (Vs. without)	↓ ACC (θ phase) ↔ DLPFC (γ amplitude) ↓ ACC (θ phase) ↔ AC (γ amplitude)
Adamchic, Toth, Hauptmann, and Tass (2014)	Intervention (ACR)	BESA (source montage) sLORETA	Distress (THI, VAS)	Post Vs. Pre treatment	↓ distress ↑ PAC (α) ↓ PAC (β,γ,δ,θ)
Adamchic et al. (2017)	Intervention (ACR)	BESA (source montage) sLORETA	Loudness (VAS)	Post Vs. Pre treatment	↓ loudness ↑ PAC (α) ↓ PAC (β,γ,δ,θ)
Balkenhol, Wallhäusser-Franke, and Delb (2013)	RS EEG	none (mean power over all electrodes)	Loudness (matching) Distress (TQ) Hearing loss (PTA)	Correlation	Loudness: ↑ γ Distress: ↑ δ,θ Hearing loss: ↓ γ
De Ridder and Vanneste (2014)	Intervention (EDS over AC)	sLORETA LPC	Loudness (VAS)	Responders (Vs. Non-Responders)	↑ l pHC (β) ↑ HC (β) ↑ AMY (β) ↑ l INS (β) ↑ pHC (γ) ↑ FPC (γ) ↑ l 2AC ↔ r pHC (δ) ↑ l 2AC ↔ r HC ↔ l pHC (θ) ↑ r PAC ↔ r pHC (β) ↑ pHC ↔ r PAC ↔ 2AC (β) ↑ pHC ↔ r PAC ↔ l 2AC (β)
De Ridder, Vanneste, Congedo, and Koenig (2011)	RS EEG with ICA	sLORETA LPC	Distress (TQ)	Correlation	↑ Comp4 (sgACC, r IFG) (α, β) ↑ sgACC ↔ pHC ↔ OFC ↔ IFG (α, β)
De Ridder et al. (2013)	Intervention (rTMS over r DLPFC)	sLORETA LPC	Loudness (VAS)	Responders (Vs. Non-Responders)	↑ r DLPFC ↔ l pHC ↔ l PAC↔ l 2AC (θ) ↑ PAC ↔ ACC ↔ pHC (θ) ↑ ACC ↔ r pHC ↔ PAC ↔ 2AC (θ)
De Ridder, Congedo, and Vanneste (2015)	RS EEG	sLORETA	Loudness (NRS) Loudness (matching)	Correlation	NRS: ↑ l aINS (α) ↑ rACC (β) ↑ dACC (β) ↑ l pHC (γ) ↑ PAC (β,γ) Matching: none
Joos et al. (2012)	RS EEG	sLORETA	Distress (NRS) Depression (BDI)	Correlation	Distress: ↑ r FPC (α,β) ↑ r OFC (α,β) ↑ sgACC (β) Depression: ↑ l FPC (α) ↑ l OFC (α)
S. H. Kim et al. (2016)	Intervention (TRT)	sLORETA LPC	Distress (THI) Loudness (NRS) Awareness (NRS)	Correlation (with improvement)	Distress: ↑ l MFG (θ) ↑ l rACC (θ) ↑ r DLPFC ↑ l INS (α) ↑ r DLPFC (α) ↑ l rACC (α) ↑ pgACC (α) ↑ l IFG (α) Loudness: ↓ r AC (γ,δ) ↓ pHC (β,δ,γ) Awareness: ↑ r rACC (θ) ↑ r DLPFC (θ) ↑ rACC (α) ↑ pgACC (α) ↑ r DLPFC (α) ↑ l OFC (γ) ↑ r MFG (γ)

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Table 2 – continued from previous page

Reference	Study Design	Source Estimation, Connectivity	Feature (Measurement)	Analysis	Findings
Meyer et al. (2014)	RS EEG	None	Distress (TQ, PRISM) Duration Loudness (VAS)	PCA Correlation (with components)	Comp *Distress* (TQ, PRISM): ↑ upper β over frontal electrodes Comp *Presence* (Duration, Loudness): ↑ δ ↑ α ↓ γ over temporal and l perisylvian electrodes
Meyer et al. (2017)	RS EEG	sLORETA	Distress (THI, TQ, PRISM) Depression (BDI) Anxiety (BAI) Health (SCL-K-9, SF-36) QOL (WHOQOL)	PCA Correlation (with components and TQ)	Comp *Distress* (THI, TQ, PRISM): ↑ INS (β) Comp *Affective disorders, health and QOL* (BDI, BAI, SCL-K-9, SF-36, WHOQOL): no correlations with EEG TQ: ↑ IPL/SMG (β) ↑ r pINS (β) ↑ r PP (β) ↑ r STG (β) ↑ INS (β)
Pierzycki et al. (2015)	RS EEG	None (mean power over all electrodes)	Distress (THI, TFI, THQ) QOL (WHOQOL) Loudness (VAS)	PCA Correlation (with components)	Comp *Tinnitus severity*: TFI, excl. auditory subscale Comp *QOL*: WHOQOL, TFI- auditory subscale Comp *Hearing*: Duration, PTA, THQ- tinnitus and hearing subscale, TFI- auditory subscale no correlations with EEG for any component
Schlee et al. (2014)	RS MEG	None	Duration	Correlation	↓ α variability over temporal sensors
Song, De Ridder, Schlee, van de Heyning, and Vanneste (2013)	RS EEG	sLORETA LPC	Age of Onset	Late (∼52y) Vs. early (∼ 29y) onset	↑ r OFC (γ) ↑ l DLPFC (β) ↑ r SMA (β) ↑ r SFG (β) ↑ r dACC (β) ↓ PCC (δ) ↓ r dPMC (θ) ↑ PAC ↔ 2AC (θ) ↑ l INS ↔ r INS (α) ↑ l INS ↔ r sgACC (α) ↑ r 2AC ↔ l PrC ↔ r PrC (α)
Song, Punte, et al. (2013)	Intervention (CI)	sLORETA LPC	Loudness (NRS) Distress (TQ)	Slight (Vs. marked) improvement	Loudness: ↑ l 2AC (δ,γ) ↑ l TP (β) ↑ l PAC ↔ r PCC (δ) Distress: ↑ l PAC ↔ r PAC (γ) ↑ r PAC ↔ l pHC (γ) ↑ r OFC ↔ l PrC (γ)
Song, Vanneste, Schlee, van de Heyning, and De Ridder (2013)	RS EEG	sLORETA LPC	Age of onset	Late (∼52y) Vs. early (∼ 29y) onset	↑ dACC (β) ↑ sgACC (β) ↑ pHC(β) ↑ r pgACC (γ) ↑ DLPFC (γ) ↑ r sgACC ↔ l PAC (γ) ↑ r MTG ↔ PAC (γ) ↑ r PCC ↔ PrC (γ) ↓ r PAC ↔ r PCC ↔ PrC (α) ↓ r PAC ↔ l PrC (β)
			Distress (TQ)	High (TQ: 47-84) Vs. low (TQ: 0-46) distress	↑ dACC (β) ↑ pgACC (γ) for late onset ↑ l OFC (β,γ,δ) ↑ l SMG (α) ↑ l DLPFC (γ) for early onset
Song et al. (2014)	RS EEG	sLORETA LPC	Hyperacusis (HQ)	With Hyperacusis (Vs. without) Correlation	Group: ↑ SMA (β) ↑ dPMC (β) ↑ dACC (β) ↑ OFC (β) ↑ r AC (α) ↑ r 2AC ↔ r PAC ↔ r PFC ↔ l sgACC ↑ l PAC ↔ l PCC Correlation: ↑ OFC (β) ↑ r AC (α) ↑ dACC (β)
Song, Vanneste, and De Ridder (2015)	RS EEG	sLORETA LPC	Awareness (%)	Correlation	↓ l dACC (δ) ↓ l pgACC (β,δ) ↓ pgACC (θ) ↓ rACC (β,δ,θ) ↓ sgACC (θ) ↓ l PAC ↔ rACC (β) ↓ l PAC ↔ sgACC (β)

Continued on next page

Table 2 – continued from previous page

Reference	Study Design	Source Estimation, Connectivity	Feature (Measurement)	Analysis	Findings
Tass et al. (2012)	Intervention (ACR)	BESA (source montage) sLORETA	Loudness (VAS) Distress (TQ)	Post Vs. Pre treatment	↓ loudness, distress ↑ PAC (α) ↓ PAC (β,γ,δ,θ)
van der Loo et al. (2009)	RS EEG	LORETA	Loudness (VAS)	Correlation	↑ contralateral PAC (γ)
van der Loo, Congedo, Vanneste, de van Heyning, and De Ridder (2011)	RS EEG	sLORETA LPC	Distress (TQ)	Correlation	↑ l aINS (α), ↑ r aINS (γ,δ) ↓ l aINS (γ,θ)
Vanneste and De Ridder (2011)	Intervention (tDCS over DLPFC)	sLORETA LPC	Distress (VAS) Loudness (VAS)	Post Vs. Pre treatment	↓ loudness, distress ↑ pgACC (α) ↓ r PAC (β,γ) ↓ iPSC (β,γ) ↑ r DLPFC ↔ pHC (θ) ↑ r PAC ↔ l pHC ↔ DLPFC ↔ pgACC (θ) ↓ DLPFC ↔ pgACC ↔ r PAC ↔ pHC (γ) ↓ l DLPFC ↔ l pHC ↔ pgACC (γ) ↓ r PAC ↔ r pHC ↔ pgACC (γ)
Vanneste and De Ridder (2012b)	Intervention (alcohol)	sLORETA	Loudness (VAS) Distress (VAS)	Post Vs. Pre treatment	↓ distress, loudness ↑ PCC (α) ↑ pgACC (β) ↑ dACC (β) ↑ l INS (β) ↓ OFC (α) ↓ VLPFC (α) ↓scACC (α) ↓ PrC (β) ↓ PrC (γ) ↓ PCC (γ)
Vanneste and De Ridder (2013)	RS EEG	sLORETA	Distress (TQ)	Correlation	↑ pgACC (α) ↑ sgACC (α)
Vanneste and De Ridder (2015)	RS EEG	sLORETA LPC	Loudness (NRS) Distress (TQ)	Correlation	Loudness: ↑ AC (β,γ) Distress: ↑ sgACC (α,β) ↑ dACC (α,β) ↑PCC (α,β) ↑ PAC ↔ sgACC ↔ d ACC ↔ PCC (α,β)
Vanneste and De Ridder (2016)	RS EEG	sLORETA LPC Granger causality	Hearing loss (PTA)	Low hearing loss Vs. Controls	↑ l aMTG(θ); ↑ l PAC ↔ r PAC (γ)
				High hearing loss Vs. Controls	↑ pHC (θ) ↑ l PAC ↔ r PAC (α,θ) ↑ l pHC ↔ r pHC (α,θ) ↑ l pHC → l PAC (θ)
				High Vs. low hearing loss	↓ l aMTG (γ); ↑ l PAC ↔ r PAC ↑ l pHC ↔ r pHC (α,θ) ↓ l pHC → l PAC (θ)
			Mean hearing loss	Correlation	↑ pHC (θ) ↑ r pHC (α) ↑ l pHC ↔ r pHC ↔ l PAC (α) ↑ l pHC ↔ l PAC ↔ r PAC (θ) ↑ r pHC ↔ l PAC (θ) ↑ l pHC → l PAC (θ)
			Range of hearing loss	Correlation	↑ pHC (α,θ) ↑ l pHC ↔ l PAC ↔ r PAC (α,θ) ↑ l pHC ↔ r pHC ↔ r PAC (α) ↑ l pHC → l PAC (θ)
			Hearing loss at tinnitus frequency	Correlation	↑ l pHC ↔ l PAC ↔ r PAC (θ) ↑ r pHC ↔ l PAC ↔ r PAC (θ) ↑ l pHC → l PAC (θ)

Continued on next page

Table 2 – continued from previous page

Reference	Study Design	Source Estimation, Connectivity	Feature (Measurement)	Analysis	Findings
Vanneste, Plazier, van der Loo, van de Heyning, Congedo, and De Ridder (2010)	RS EEG	LORETA	Distress (TQ)	High Vs. low distress High distress Vs. controls	↑ scACC (α) ↑ INS (α) ↑ pHC (α) ↑ AMY (α) ↓ PCC (α) ↓ PrC (α) ↓ DLPFC (α) ↑ dACC (α,β) ↓ dACC (δ,θ)
Vanneste, Plazier, van der Loo, van de Heyning, and De Ridder (2010)	RS EEG	sLORETA	Type	Narrow-band noise (Vs. pure tone)	↑ PCC (β) ↑ r HC (β) ↑ r pHC (γ) ↓ r lFPC (δ)
Vanneste, Focquaert, van de Heyning, and De Ridder (2011)	Intervention (tDCS over DLPFC)	sLORETA LPC	Distress (VAS) Loudness (VAS)	Responders (Vs. Non-Responders)	↑ r PAC (γ) ↑ r 2AC (γ) ↑ pHC (γ) ↑ r DLPFC ↔ r pHC (γ) ↑ r DLPFC ↔ sgACC (γ)
Vanneste, Plazier, van der Loo, van de Heyning, and De Ridder (2011)	RS EEG	sLORETA	Location	Uni- (Vs. bi-) lateral Bi- (Vs. Controls) Uni- (Vs. Controls)	↑ VLPFC (δ) ↑ pHC (β,γ) ↑ AG (β,γ) ↑ AC (β,γ) ↓ sPMC (β) ↑ VLPFC (β) ↑ FPC (β) ↑ sPMC (γ) ↑ r sPMC(γ)
Vanneste, van de Heyning, and De Ridder (2011a)	RS EEG	sLORETA	Location	Left- and right-sided	↑ contralateral pHC (γ)
Vanneste, van de Heyning, and De Ridder (2011b)	RS EEG	sLORETA LPC	Duration	Recent onset (Vs. chronic: >4 years)	↑ SMA (θ) ↑ dACC (β) ↑ INS (β) ↑ PAC (γ) ↑ 2AC (γ) ↑ l pHC ↔ l PAC ↔ l 2AC ↔ l INS ↔ r DLPFC (γ) ↓ connectivity in general (α,γ,θ)
Vanneste et al. (2012)	RS EEG	sLORETA LPC	Gender	Females (Vs. Males)	↑ OFC (β) ↑ FPC (β) ↑ OFC ↔ INS ↔ sgACC ↔ pHC ↔ PAC ↔ 2AC (α)
Vanneste et al. (2013)	Intervention (music)	sLORETA	Depression (HADS) Loudness (VAS) Annoyance (VAS)	Post Vs. Pre treatment	only group using music to overcompensate hearing loss: ↑ loudness, annoyance, depressive feelings ↑ l dACC (α) ↑ l pgACC (β) ↑ PAC (γ)
Vanneste, Congedo, and De Ridder (2014)	RS EEG with ICA	sLORETA LPC	Distress (TQ)	Correlation	↓ Comp1 (PCC, PrC) (α,β) ↓ Comp2 (PCC, PrC, IPL, pHC) (α,β,γ) ↑ Comp4 (pgACC, sgACC, VMPFC, INS) (α) ↑ Comp6 (dACC, SMA, sgACC, VMPFC, MFG) (β)
			Loudness (VAS)	Correlation	Comp1 ↔ Comp2 ↔ Comp4 ↔ Comp6 (α,δ,θ) Comp3 ↔ Comp5 (γ) ↓ Comp3 (rsPCC, LG, pHC) (β) ↑ Comp5 (sgACC, VMPFC, HC, AMY, MFG) (β)
Vanneste, Joos, Langguth, To, and De Ridder (2014)	RS EEG	sLORETA LPC	Coping style Distress (TQ) Loudness (VAS) Depression (BDI)	Mal- (Vs. adaptive) coping Correlation	Group: ↑ loudness, distress, depression ↑ l DLPFC (α) ↑ sgACC (α) ↑ connectivity in default mode network Correlations: ↑ DLPFC (α) with maladaptive coping ↑ sgACC (α) with distress and depression

Continued on next page

Table 2 – continued from previous page

Reference	Study Design	Source Estimation, Connectivity	Feature (Measurement)	Analysis	Findings
Vanneste, Faber, Langguth, and De Ridder (2016)	RS EEG	sLORETA	Cognition	Correlation	↑ HC (β) ↑ pgACC (β) ↑ sgACC (β) ↑ r INS (β)

Note. ↑, increase / positive correlation; ↓, decrease / negative correlation; ↔, functional connectivity between x and y; →, effective connectivity from x to y; l, left; r, right; 2AC, secondary auditory cortex; AC, auditory cortex; ACC, anterior cingulate cortex; ACR, acoustic coordinated reset; AG, angular gyrus; aINS, anterior insula; aMTG, anterior middle temporal gyrus; AMY, amygdala; BAI, Beck's Anxiety Inventory (A. T. Beck, Epstein, Brown, & Steer, 1988); BDI, Beck's Depression Inventory (A. T. Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); CFC, cross-frequency coupling; CI, cochlear implantation; Comp, Component; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; dPMC, dorsal premotor cortex; EDS, extradural stimulation; FPC, frontopolar cortex; HC, hippocampus; ICA, independent component analysis; IFG, inferior frontal gyrus; INS, insula; IPL, inferior parietal lobule; iPSC, inferior primary somatosensory cortex; lFPC, lateral frontopolar cortex; LG, lingual gyrus; LPC, lagged phase coherence; MFG, middle frontal gyrus; MTG, middle temporal gyrus; NRS, numeric rating scale; OFC, orbitofrontal cortex; PAC, primary auditory cortex; PCA, principal component analysis; PCC, posterior cingulate cortex; PFC, prefrontal cortex; pgACC, pregenual anterior cingulate cortex; pHC, parahippocampus; pINS, posterior insula; PMC, premotor cortex; PP, planum parietale; PrC, precuneus; PRISM, Pictorial Representation of Illness and Self-Measure (Büchi, Sensky, Sharpe, & Timberlake, 1998); PTA, pure tone audiometry; QOL, quality of life; rACC, rostral anterior cingulate cortex; RS, resting-state; rsPCC, retrosplenial posterior cingulate cortex; rTMS, repetitive transcranial magnetic stimulation; scACC, subcallosal anterior cingulate cortex; SCL-K-9, Symptom Check List short form (Klaghofer & Brähler, 2001); SF-36, Short Form Health Survey (Ware Jr & Sherbourne, 1992); SFG, superior frontal gyrus; sgACC, subgenual anterior cingulate cortex; SMA, supplementary motor area; SMG, supramarginal gyrus; sPMC, superior premotor cortex; STG, superior temporal gyrus; TC, temporal cortex; tDCS, transcranial direct-current stimulation; TF, Tinnitus Functional Index (Meikle et al., 2012); THI, Tinnitus Handicap Questionnaire (Newman et al., 1996); THQ, Tinnitus Handicap Questionnaire (Kuk, Tyler, Russell, & Jordan, 1990); TP, temporal pole; TQ, Tinnitus Questionnaire (Goebel & Hiller, 1994); TRT, tinnitus retraining therapy; VAS, visual analogue scale; VMPFC, ventromedial prefrontal cortex; WHOQOL, World Health Organization Quality of Life assessment (short form).

2.2 Article II: Individualized alpha/delta neurofeedback protocols lead to stable alleviation of tinnitus-related distress.

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Abstract *Background:* First attempts have demonstrated that the application of alpha/delta neurofeedback in the treatment of chronic tinnitus leads to a reduction of symptoms at group-level. However, recent research suggests that chronic tinnitus is a very heterogeneous phenomenon that requires treatment of distinct subgroups or even individually tailored treatment. *Objective:* The purpose of this study was to evaluate an individually adjusted neurofeedback protocol aimed at increasing alpha and decreasing delta power. Unlike in previous studies, the frequency range for the rewarded alpha band was not set on the fixed alpha band but rather determined on an individualized basis according to the individual alpha peak frequency (IAF) of each patient. *Methods:* Twenty-six chronic tinnitus patients participated in 15 weekly neurofeedback training sessions and extensive pre- and post-tests, as well as follow-up testing (3 and 6 months after the training). The main outcome measures

of this study consisted of tinnitus-related distress measured with the Tinnitus Handicap Inventory (THI) and Tinnitus Questionnaire (TQ), tinnitus loudness, and pre- and post-training resting-state EEG activity in trained frequency bands. *Results:* The applied neurofeedback protocol led to a significant reduction of tinnitus-related distress and tinnitus loudness. While distress remained on a low level even 6 months after the completion of training, loudness returned to baseline levels in the follow-up period. In addition, resting-state EEG activity showed an increase in the trained alpha/delta ratio over the course of the training. Furthermore, this ratio increase was related to training-induced changes of tinnitus-related distress as measured with TQ, mainly due to increases in the alpha frequency range. *Conclusion:* This study confirms alpha/delta neurofeedback as a suitable option for the treatment of chronic tinnitus and represents a first step towards the development of individual neurofeedback protocols.

Keywords: Tinnitus, neurofeedback, EEG, alpha, IAF, delta, loudness, distress

2.2.1 Introduction

Approximately 5-15% of the Western population suffer from a permanent sensation of ringing or hissing in their ears, also known as chronic subjective tinnitus (Henry et al., 2005). Many affected people suffer considerably from the constant sound perception which in some cases means a considerable reduction of quality of life. Often, chronic tinnitus induces related issues which include sleeping or concentration problems, difficulties in social interactions, severe depression or anxiety impairments (Dobie, 2003; Heller, 2003; Langguth, Landgrebe, Kleinjung, Sand, & Hajak, 2011). An effective treatment to completely alleviate tinnitus symptoms has not yet been discovered, and many sufferers do not receive the help they need. As a consequence, this lack of a sustained effective interventions can lead to increased stress and frustration, and may then have a further negative impact on the quality of life of many patients (Holmes & Padgham, 2008).

While subjective tinnitus was first assumed to be a problem of the peripheral hearing system only (Eggermont, 1990; Møller, 1984), it is currently widely regarded as an auditory phantom percept emerging from unsuccessful compensatory mechanisms in the brain as a result of inner ear receptor damage (Eggermont & Roberts, 2004; Elgoyhen et al., 2015; Langguth et al., 2013). Electrophysiological recordings with electroencephalography (EEG) or magnetoencephalography (MEG) have led to the proposal of tinnitus-related abnormalities in spontaneous resting-state brain activity. According to recent studies, the resting brain of tinnitus patients when compared to healthy control subjects, typically shows enhanced activity in delta (0.5-4 Hz) and gamma (35.5-45 Hz) frequency bands over temporal areas, with reduced amounts of alpha (8.5-12 Hz) oscillations (Adjamian et al., 2009; Ashton et al., 2007; Kahlbrock & Weisz, 2008; Lorenz et al., 2009; Schlee et al., 2008; Weisz, Dohrmann, & Elbert, 2007; Weisz, Moratti, et al., 2005; Weisz, Müller, et al., 2007). The theoretical framework for these findings is provided by the thalamocortical dysrhythmia (TCD) model (Llinás et al., 1999) and the synchronization-by-loss-of-inhibition model (SLIM) (Weisz, Dohrmann, & Elbert, 2007). The TCD model describes the emerging of spontaneous firing of thalamic fibers due to auditory input deprivation as an essential factor for tinnitus genesis (Llinás et al., 1999). If thalamic relay cells are deprived of excitatory sensory input from the inner ear, the hyperpolarized cell membrane causes these neurons to fire low-threshold calcium spike bursts in a slow-wave mode. Thalamocortical feedback loops then lead to the establishment of this slow-wave rhythm in cortical neurons, which is measurable as ongoing delta activity on the scalp. Llinás et al. (1999) further propose an *edge effect* resulting from increased gamma oscillations to be responsible for perceptive distur-

bances such as tinnitus. Furthermore, it is suggested in the SLIM that this increase in gamma frequency range may additionally be driven by decreased lateral inhibition processes in auditory cortex areas due to under-activation of inhibitory neurons (Weisz, Dohrmann, & Elbert, 2007). This imbalance between cortical inhibition and excitation might thus provide an explanation for the alpha-down, delta-up pattern typically found in resting-state M/EEGs of tinnitus patients (De Ridder, Vanneste, Langguth, & Llinás, 2015).

Neurofeedback has recently gained increased attention in the treatment of a variety of psychological and neurological disorders. In the process of neurofeedback, electrophysiological brain activity is recorded non-invasively and then directly fed back to the subject in real time. The reward of wanted and inhibiting of unwanted changes in the signal pattern by providing directly perceivable visual, auditory, and/or tactile feedback is proposed to trigger a learning process during which patients learn how to voluntarily control their brain activity and adjust it in the desired direction. Neurofeedback has continued to be developed since the late 1960s (Sterman & Friar, 1972; Wyrwicka & Sterman, 1968) and is today an established treatment method in the field of attention deficit hyperactivity disorder (ADHD) (Arns et al., 2009; Gevensleben et al., 2009; Lévesque et al., 2006; J. F. Lubar et al., 1995; Strehl et al., 2017). Furthermore, first attempts have been made to implement it in an effective treatment for chronic tinnitus (for a review, see Güntensperger, Thüring, Meyer, Neff, & Kleinjung, 2017). In this context, the training of frequency bands linked to the aforementioned abnormalities in resting-state brain activity has been shown to be a highly promising approach. Two research groups reported that neurofeedback training aimed at increasing alpha and decreasing delta activity over auditory areas led to significant reductions in tinnitus-related symptoms (i.e., tinnitus distress and loudness) and that these behavioral changes were also linked to the trained resting-state activity (Crocetti et al., 2011; Dohrmann, Elbert, et al., 2007). Gamma has been largely neglected in neurofeedback treatments for chronic tinnitus. The reason for this is the current discussion that gamma may reflect an attempt of the brain to suppress tinnitus rather than causing it (Sedley & Cunningham, 2013; Sedley et al., 2012) or may be involved in the communication of prediction errors (Sedley et al., 2016). Given these inconsistencies, the specific role of gamma oscillations for tinnitus need to be better explored in order to justify their consideration for neurofeedback protocols.

The aim of this clinical study is to contribute to the development of effective neurofeedback protocols for tinnitus patients and to build on as well as extend the previously applied auditory alpha/delta training. For the recording of brain activity

used for the feedback, the same EEG electrodes (FC1, FC2, F3, F4) were chosen as in the aforementioned studies (Crocetti et al., 2011; Dohrmann, Elbert, et al., 2007) to guarantee comparability. Regarding the frequency bands used for the training, however, a novel approach was favored. It has recently been clarified that chronic tinnitus is a very multifaceted and complex phenomenon (e.g., Landgrebe et al., 2010; Langguth et al., 2013). For this reason, it is of the utmost importance to consider neurofeedback treatment on a more individualized basis in order to appropriately meet the specific needs of each tinnitus patient. With this project, we aim to make the first step in this direction. In particular, we follow observations that the individual alpha peak frequency (IAF) can vary considerably among individuals (Klimesch, 1999). Using the fixed alpha band (generally defined between 8 and 12 Hz) for power analysis, therefore, does not reflect alpha-band power for each subject appropriately. We thus suggest that these inter-individual differences have to be considered when alpha is targeted in a neurofeedback training protocol. Furthermore, a recent study with tinnitus patients underlined the importance of taking this inter-individual alpha variability into account in this group (Schlee et al., 2014). This is the reasoning behind why we did not choose the standard alpha band (8-12 Hz) as a fixed reward frequency range for each patient, as has customarily been done in previous studies. Instead, an individual alpha peak frequency was determined for each tinnitus patient before the first neurofeedback session and an individually adjusted alpha band used for generating neurofeedback reward.

In addition, we put great emphasis on making our results replicable and comparable to other studies. Accordingly, we designed our study closely following the guidelines of the Tinnitus Research Initiative (TRI) (Landgrebe et al., 2012; Langguth et al., 2007) on outcome measures for tinnitus intervention studies. We thus combined our training with a wide variety of questionnaires and tests at different time points while also using different measurements for tinnitus-related distress and other health-related variables. In addition, the classical pre-post design, generally used in treatment studies, was enriched with two follow-up measurements in order to investigate longevity and persistence of the potential effects. Main behavioral outcome measures of this study were tinnitus-related distress, measured with two well-established tinnitus questionnaires, and tinnitus loudness. Both variables were hypothesized to decrease over the course of the neurofeedback training and to remain on a stable lower level at the follow-up time-points. Furthermore, in order to examine whether the neurofeedback training indeed evoked the desired effects in EEG activity, the ratio between the rewarded alpha- and the inhibited delta-band was compared across time-points. It was expected that the alpha/delta ratio would change significantly between pre- and post-tests and would remain on a stable level

in the follow-up period.

2.2.2 Materials and methods

2.2.2.1 Participants

Participants were recruited at the Department of Otorhinolaryngology (University Hospital Zurich). In order to be eligible for study inclusion, patients had to be diagnosed with chronic subjective tinnitus (> 0.5 years), be between 18 and 75 years old, have adequate knowledge of the German language, suffer from no other psychiatric or neurological disorder, and have no acute suicidal tendency. Furthermore, patients with drug or alcohol addiction, cochlear implants, and current prescriptions for tranquilizers, neuroleptics, or antiepileptics were not considered. It should be mentioned that this study is part of a comprehensive clinical project, and participants were randomly assigned to one of two study groups (single-blind randomized controlled trial). Both groups underwent the exact same procedure (see section 2.2.2.2) with the sole difference being a technical aspect of feedback generation. The group reported here followed neurofeedback application closely related to prior studies (see section 2.2.2.5) in which the activity included for calculating reward and inhibit rates was limited to four electrodes. The other group used a marginally different approach in that more EEG electrodes in addition to source estimation algorithms were involved in feedback generation. The results of this group as well as between-group comparisons will be discussed elsewhere. According to the aforementioned criteria, 26 suitable patients with chronic subjective tinnitus were identified and included. Participants were between 24 and 71 years old with a mean age of 46.15 ($SD = 12.33$). The sample consisted of 20 males and 6 females. The study was approved by the appropriate Ethics Committee (Kantonale Ethikkommission Project KEK-ZH-Nr. 2014-0594), and was online registered at ClinicalTrials.gov (NCT02383147) and kofam.ch (SNCTP000001313).

2.2.2.2 Procedure

This prospective clinical trial consisted of 20 visits in total. In the first appointment, 1-2 weeks before the start of the neurofeedback training phase, patients were extensively informed about the purpose and exact procedure of the study, and signed their informed consent in the presence of a qualified medical professional at the Department of Otorhinolaryngology. In the same visit, participants further underwent the audiometric screening in which their pure tone hearing thresholds at 0.25, 0.5, 1, 2, 4, 6, and 8 kHz as well as other audiometric measurements (speech audiogram

and speech-in-noise test) were determined. In the second screening visit, a baseline resting-state EEG measurement was performed and patients were asked to complete questionnaires covering demographics and tinnitus-related symptoms, as well as several other psychological and health-related questions (details in section 2.2.2.3).

After the two baseline appointments (t1), patients participated in a total of 15 neurofeedback training sessions on a weekly basis. Occasional re-scheduling of individual sessions as well as absences due to holidays or illness were unavoidable and compensated for as best as possible. One week after the completion of the training period, a post-measurement was performed (t2) consisting of the repeated measurement of 16 minutes of resting-state EEG and completion of the questionnaires. The same procedure was repeated around 3 months later when the first follow-up measurement was conducted (t3). In the final follow-up (t4), 6 months after the end of the training period, patients received a link by email and were asked for another completion of the set of questionnaires online. Subsequently, they were informed that they had fully completed the clinical study and were provided the opportunity to discuss their individual results with the study team.

2.2.2.3 Behavioral measurements

The set of questionnaires consisted of a variety of forms according to the guidelines of the Tinnitus Research Initiative (TRI) (Landgrebe et al., 2012; Langguth et al., 2007). In particular, an adjusted version of the Tinnitus Sample Case History Questionnaire (TSCHQ) was used to ask about demographics, tinnitus properties (e.g., origin, location, loudness, type), prior treatment attempts, and other tinnitus-related issues. Two questionnaires were used to assess tinnitus distress: the Tinnitus Handicap Inventory (THI) (German version by Kleinjung, Fischer, et al., 2007) and Tinnitus Questionnaire (TQ) (German version by Goebel & Hiller, 1994). Sum-scores can be calculated for both questionnaires ranging from 0-100 in the former, and 0-84 in the latter case. In addition, the TQ score can be divided into the six sub-scores “emotional distress”, “cognitive distress”, “intrusiveness”, “auditory perceptual difficulties”, “sleep disturbances”, and “somatic complaints”.

Additionally, participants completed German versions of Beck’s Depression Inventory (BDI) (Hautzinger, Bailer, Worall, & Keller, 1995), Beck’s Anxiety Inventory (BAI) (Prinz & Petermann, 2015), the short form of the WHO Quality of Life scale (WHOQOL-BREF) (Angermeyer, Kilian, & Matschinger, 2000), Symptom Check List (SCL-K-9) (Klaghofer & Brähler, 2001), and Short Form Health Questionnaire (SF-36) (Bullinger, Kirchberger, & Ware, 1995). Completion of ques-

tionnaires took about 45 minutes in total and was done electronically on an iPad during the preparation of the EEG system at t1, t2 and t3, and online via an email-link at t4.

The main behavioral outcome measures of this study are tinnitus loudness (rated from 1 "very low" to 100 "very high"), sum-score of the THI, and sum- as well as sub-scores of the TQ.

2.2.2.4 EEG recording

BrainAmp DC amplifier system in combination with 64 active channel actiCap electrode caps (Brain Products, Munich, Germany) were used to record resting-state EEG at t1, t2, and t3. The array of silver/silver chloride electrodes corresponded with the 5/10 electrode position system (Oostenveld & Praamstra, 2001). Recording was referenced against the FCz electrode with a ground electrode positioned at AFz position. A sampling rate of 1000 Hz was used; the electrodes were prepared with conductive paste for recording, and impedance was kept below 10 kΩ. Recordings were done in direct current (DC) mode with no online filters applied. Patients were asked to sit upright on a comfortable chair in a sound-proof and electromagnetically shielded room and to avoid excessive movements and muscle contractions in order to minimize artifacts. During recording, subjects were instructed by a pre-recorded voice to open (EO) and close (EC) their eyes in regular intervals. For playback of these instructions, Presentation software (Neurobehavioral Systems, Inc., 2010) was used, and a fixation cross was presented during eyes-open segments. Resting-state EEG was recorded twice over a time span of 8 minutes. While in the first 8 minutes of recording no additional instructions were given (EEG with no task: EEG-NT), in the second measurement patients were asked to deliberately not suppress their tinnitus (EEG with task: EEG-WT). This was done to control for unwanted suppression effects that happen continuously in the brains of tinnitus sufferers (see also, Sedley & Cunningham, 2013). According to the recommendations of Working Group 3 of the European tinnitus research network, TINNET (http://www.tinnet.tinnitusresearch.net/), resting-state activity of eyes-open segments was chosen as the main electrophysiological outcome measure.

2.2.2.5 Neurofeedback training

EEG for neurofeedback training was registered with four silver/silver chloride electrodes, FC1, FC2, F3, and F4 combined with a NeuroAmp amplifier (BEE Medic GmbH, Singen, Germany). Electrodes at the earlobes served as reference electrodes, and AFz as ground electrode. In addition, the sampling rate was set at 500 Hz,

impedance was kept below 20 kΩ, the EEG signal was processed in real-time using the software Cygnet 2.0.3.34 (EEG Info, Kirchberg, Switzerland), and the feedback was implemented in the computer simulation Inner Tube (Somatic Vision, Encinitas, CA, USA). In this visualization, patients observed a space ship automatically navigating through a narrow tunnel. While increased power in the alpha band led to acceleration of the ship, delta as the defined inhibited band was linked to autopilot accuracy. It is important to note that automatic filtering is included in the Cygnet software so that any kind of movement artifacts (blinking included) as well as system voltage (45-55 Hz) are automatically detected and excluded from feedback.

In the first neurofeedback training session, an individual alpha peak was determined for each participant by averaging alpha peaks over 30 seconds of resting-state EEG (Klimesch, 1999). Subsequently, the reward frequency was set in the range of ±2 Hz around this peak frequency. On the other side, the frequency range of 3-4 Hz corresponding to the delta band was generally set to evoke negative feedback. Patients were asked to sit comfortably in a chair, avoid excessive muscle movement and pay close attention to the feedback game. Following the custom of previous studies (Crocetti et al., 2011; Dohrmann, Elbert, et al., 2007), no further instruction was given as to how to influence the feedback or what strategy to use in order to allow for the highest amount of freedom possible. The training itself lasted 15 minutes and was repeated once a week, preferably on the same weekday at the same time.

2.2.2.6 Data analysis

EEG preprocessing Preprocessing of EEG data was done with BrainVision Analyzer 2 (Brain Products, Munich, Germany). Data was first band-pass filtered with Butterworth zero-phase filers between 0.1 Hz and 80 Hz with slopes of 24 dB/octave at the low, and 48 dB/octave at the high cutoffs. In order to eliminate possible line noise, data was further filtered with a band-rejection filter with a central frequency of 50 Hz, a bandwidth of 1 Hz, and a slope of 24 dB/octave. The EEG signal was split into independent components in order to identify regular artifacts (e.g., eye-blinks, pulse artifacts, noise). This was done by applying an independent component analysis (ICA) with a restricted Infomax algorithm implemented in BrainVision Analyzer 2. Bad (i.e., very noisy or dead) channels were temporarily excluded from this step. With the inverse ICA procedure, the resulting components indicative of artifacts were removed from the data. Subsequently, spline-type topographical interpolations were performed for previously excluded channels and channels with remaining noise. A thorough visual inspection was performed in order to remove remaining vertical artifacts (i.e., muscle movements, short drifts or jumps over single or multi-

ple electrodes) from the signal. An average reference over all channels was calculated and applied whereby the implicit reference of data recording (FCz) was re-included into the data and used for subsequent analysis. Finally, data was segmented into eyes closed and eyes open conditions and imported to MATLAB Statistics Toolbox Release 2017a (The MathWorks Inc., Natick, Massachusetts, United States) and EEGLAB 14.1.1b (Delorme & Makeig, 2004).

EEG analysis A hamming window with 2s window length and 1s overlap was first applied on the data of eyes-closed and eyes-open segments. Subsequently, Fast Fourier Transform (FFT) was computed for each 2s-segment, logarithmized, and then averaged over all segments for each patient. The resulting values provided power values in decibel (dB) for each electrode of the EC/EO segments of each measurement (EEG-NT and EEG-WT). The frequency resolution was thus 0.5 Hz. Next, we calculated alpha/delta ratio by dividing power values in the rewarded (individual) alpha range by those in the inhibited delta range (3-4 Hz). This ratio was finally averaged over the four electrodes used for training (FC1, FC2, F3, F4) as well as over all 65 electrodes of the EEG system. In addition, power values in standard frequency bands delta (0.5-4 Hz), theta (4.5-8 Hz), lower alpha (8.5-10 Hz), upper alpha (10.5-12 Hz), alpha (8.5-12 Hz), beta1 (12.5-15 Hz), beta2 (15.5-23 Hz), beta3 (23.5-35 Hz), and gamma (35.5-45 Hz) were calculated and analyzed.

Statistics Data was analyzed using the software package R (R Core Team, 2017) including packages "ggplot2" (Wickham, 2009), "ggsignif" (Ahlmann-Eltze, 2017), "Hmisc" (Harrell Jr, 2017), "jtools" (Long, 2017), "multcomp" (Hothorn, Bretz, & Westfall, 2008), "nlme" (Pinheiro, Bates, DebRoy, Sarkar, & R Core Team, 2017), and "xtable" (Dahl, 2016). Repeated-measures mixed model analysis of variance (ANOVA) was used to estimate time effects for behavioral (THI sum-score, TQ sum- and sub-scores, tinnitus loudness) and EEG-related data. A priori defined contrasts comparing t1 with all other time-points (t2, t3, t4 for behavioral measures; t2, t3 for EEG data) were calculated to gain insight into training success and the stability of changes in the follow-up period. Since contrasts are not independent, Bonferroni correction was applied, and, because the contrasts were set a priori, one-tailed p-values are here reported. Effect size r for a priori defined contrasts are reported and these were directly converted from respective t-values according to Field, Miles, and Field (2012, p.580-581). Cohen (1988) suggests that $r = 0.1$ may be labelled a small, $r = 0.3$ a medium, and $r = 0.5$ a large effect. In addition, post-hoc Tukey tests were performed comparing each of the four time-points with each other in order to reveal other potential differences between time-points. In order to test for relationships between changes in the behavioral and electrophysiological domain,

Pearson product-moment correlation coefficients between difference scores (t2-t1) were calculated and tested for statistical significance. The alpha threshold was set at $p = .05$ for all statistical tests.

2.2.3 Results

2.2.3.1 Behavioral results

Baseline Two patients who completed the full study procedure had to be excluded from data analysis because their BDI scores at all four time points suggested clinically relevant depressive symptoms (i.e., a sum-score of more than 18 points). The final sample size for data analysis was therefore reduced to 24 participants. Table 3 shows the demographic and clinical details of the participants included in the final analysis. The study sample had a mean age of 46.29 ($SD = 12.22$) and consisted of 19 males and 5 females. All participants were right-handed, most of them (n=15) had a degree in higher education, and were working full- or part-time (n=14). Mean hearing loss across all tested frequencies was 7.54 dB ($SD = 8.25$).

Mean tinnitus duration of the study sample was 78.92 months ($SD = 74.63$), and the mean age of onset was 39.75 years ($SD = 14.66$). Most participants (n=6) named stress as the primal cause of tinnitus, and the percept was mostly tonal (n=17) with a pitch described as "very high" in 12 subjects. Almost all (n=21) perceived tinnitus in both ears, however 9 subjects of this group indicated a left- while 6 specified a right-sided tendency. Mean tinnitus loudness was rated as 53.25 ($SD = 19.57$), while mean distress measured with the THI consisted of 29.33 ($SD = 14.7$) points, and of 23.75 ($SD = 11.63$) points with the TQ, respectively. These values suggested a "mild tinnitus" according to the THI and a "slight tinnitus" according to the TQ for the overall group on average. All tinnitus-related measures were significantly positively correlated (THI and TQ: $r(22) = 0.8$, $p < .001$; THI and loudness: $r(22) = 0.47$, $p = .022$; TQ and loudness: $r(22) = 0.56$, $p = .004$).

Pearson correlations between tinnitus- and health-related measures are summarized in Table 4. All correlations are corrected for multiple comparisons using the method of Benjamini and Hochberg (1995). Notably, depressive symptoms as measured with the BDI were positively correlated with THI, $r(22) = 0.75$, $p < .001$, as well as TQ sum-scores, $r(22) = 0.79$, $p < .001$ but not loudness, $r(22) = 0.48$, $p = .052$. Furthermore, significant negative correlations were observed between quality of life as measured with the psychological health domain of the WHOQOL-BREF (domain 2) and all tinnitus-related measures (THI: $r(22) = -0.63$, $p = .004$; TQ: $r(22) = -0.55$, $p = .021$; Loudness: $r(22) = -0.52$, $p = .029$). Moreover, significant

Table 3: Demographics, Health and Tinnitus Characteristics of Study Sample

	Mean	SD[a]	Median	Min	Max
Age	46.29	12.22	44	24	71
Mean Hearing Loss (dB)	7.54	8.25	4.4	0	22.8
Tinnitus Duration (months)	78.92	74.63	40	18	312
Age of Onset	39.75	14.66	39	14	67
Tinnitus Loudness (0-100)	53.25	19.57	50	20	95
Tinnitus Distress (THI)	29.33	14.7	27	4	56
Tinnitus Distress (TQ)	23.75	11.63	23	6	45
BDI sum-score[b]	6.29	4.34	7	0	13
BAI sum-score[b]	7.12	5.77	6.5	0	21
WHOQOL-BREF Domain 1: Physical Health[c]	76.49	14.48	79	43	100
WHOQOL-BREF Domain 2: Psychological Health[c]	69.97	15.78	69	42	96
WHOQOL-BREF Domain 3: Social Relationship[c]	66.32	19.73	67	25	100
WHOQOL-BREF Domain 4: Environment[c]	81.51	11.28	84	62	100
WHOQOL-BREF Global Value[c]	67.19	18.36	62	25	100
SCL-K-9[d]	0.72	0.71	1	0	3
SF-36: Mental Health[e]	45.79	9.46	47	22	60
SF-36: Physical Health[e]	53.38	6.76	55	35	60

Note. [a]SD=Standard Deviation. [b]Sum-scales (0-84) measuring severity of depressive/anxiety symptoms. [c]Scaled sum-scores (0-100) indicating quality of life in specific domains or globally. [d]Mean over all items (0-4) measuring general psychological strain. [e]Normed sum-scales (M = 50, SD = 10) indicating mental/physical disability; higher values indicate less disability.

negative correlations were found between the mental health score of SF-36 with THI-, $r(22)$ = -0.69, p = .002, and TQ- sum scores, $r(22)$ = -0.66, p = .003.

Training effects Results concerning changes in tinnitus-related symptoms are summarized in Figure 5. Repeated-measures mixed model ANOVA suggested significant effects of the factor *time* on tinnitus-related distress measured with the THI, $\chi^2(3) = 9.18$, p = .027, and tinnitus loudness, $\chi^2(3) = 12.4$, p = .006. Results for the TQ, on the other hand, did not suggest significant differences over time, $\chi^2(3) = 5.24$, p = .155. However, an ANOVA performed on the sub-scores of TQ revealed significant time effects for "emotional distress", $\chi^2(3) = 8.94$, p = .03.

A priori defined contrasts showed a significant decrease between t1 (M = 29.33,

Table 4: Pearson Correlation between Tinnitus and Health Questionnaires

	THI	TQ	Loudness
BDI sum-score	0.75***	0.79***	0.48
BAI sum-score	0.34	0.41	−0.03
SCL-K-9	0.47	0.56*	0.30
WHOQOL-BREF Domain 1: Physical Health	−0.65 **	−0.42	−0.37
WHOQOL-BREF Domain 2: Psychological Health	−0.63 **	−0.55 *	−0.52 *
WHOQOL-BREF Domain 3: Social Relationship	−0.30	−0.24	−0.19
WHOQOL-BREF Domain 4: Environment	−0.16	−0.11	−0.13
WHOQOL-BREF Global Value	−0.51 *	−0.25	−0.20
SF-36 Physical Health	−0.43	−0.22	0.02
SF-36 Mental Health	−0.69 **	−0.66 **	−0.45

Note. Pearson correlation coefficient corrected for multiple comparisons with the method of Benjamini and Hochberg (1995). $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

SD = 14.7) and t2 (M = 23.92, SD = 12.71) for THI-measured distress, $t(69)$ = -2.76, p = .011 (one-tailed). This THI decline stayed significant at t3, the 3-month follow-up (M = 24.83, SD = 12.48), $t(69)$ = -2.3, p = .037 (one-tailed), as well as at t4, 6 months after the training (M = 24.75, SD = 16.48), $t(69)$ = -2.34, p = .033 (one-tailed). A post-hoc Tukey test corroborated these three significant results and revealed no further significant differences. Effect sizes were r = 0.32 for t1-t2, r = 0.27 for t1-t3, and r = 0.27 for t1-t4, and effects can thus be considered small to medium.

Even though the main analysis did not reveal a significant effect for the TQ, the sum-score measured prior to the neurofeedback training at t1 (M = 23.75, SD = 11.63) was found to be significantly higher than the average over the three time-points after neurofeedback (M = 21.25, SD = 12.01), $t(69)$ = -2.14, p = .018 (one-tailed). Furthermore, the contrast between t1 and t4 (M = 20.58, SD = 12.81) reached statistical significance, $t(69)$ = -2.21, p = .046 (one-tailed). Differences between t1 and t2 (M = 21.62, SD = 12.03), $t(69)$ = -1.48, p = .214 (one-tailed), as well as between t1 and t3 (M = 21.54, SD = 11.18), $t(69)$ = -1.54, p = .192 (one-tailed) were not significant. With the Tukey post-hoc test no other significant differences were found. Effect sizes for the TQ were r = 0.18 for t1-t2, r = 0.18 for t1-t3, and r = 0.26 for t1-t4.

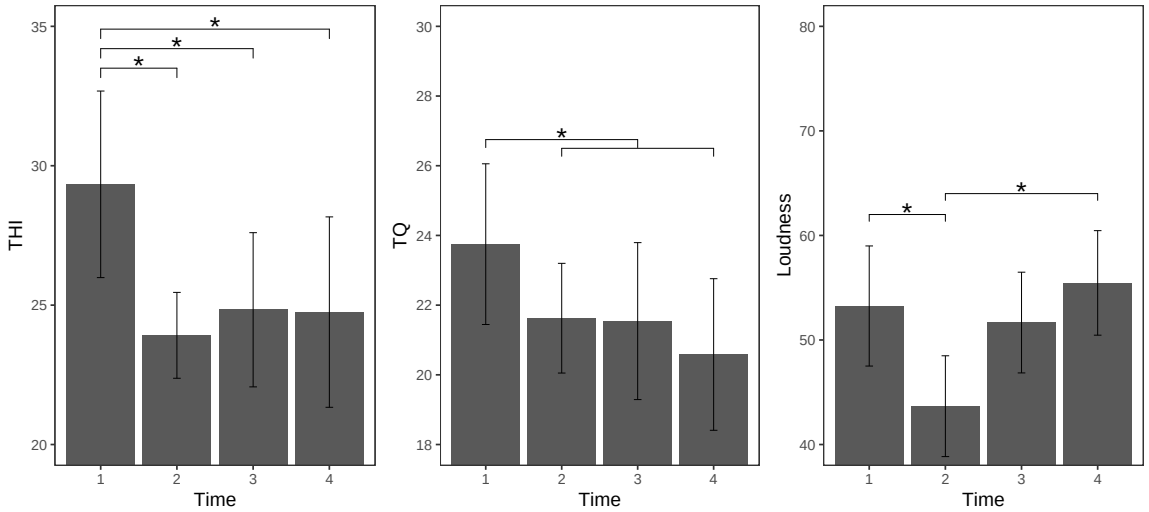

Figure 5: Barplots showing tinnitus-related symptoms before (t1), 1 week after (t2), 3 months after (t3), and 6 months after (t4) neurofeedback training. Error bars represent ±1 standard error for within-subjects designs according to Morey (2008). THI scores showed significant decreases from t1 to t2, and differences between t1 and the two follow-up time-points were significant. TQ scores were significantly higher at t1 compared to the other three time-points combined. For tinnitus loudness a significant decrease between t1 and t2 was found followed by a significant increase to t4.

For rated tinnitus loudness, a priori defined contrasts revealed a significant decline between t1 (M = 53.25, SD = 19.57) and t2 (M = 43.67, SD = 22.42), $t(69)$ = -2.74, p = .012 (one-tailed). The effect size of this result was r = 0.31. The other differences between t1 and t3 (M = 51.67, SD = 22), $t(69)$ = -0.45, p = .978 (one-tailed), and between t1 and t4 (M = 55.46, SD = 17.28), $t(69)$ = 0.63, p = 1.588, were not significant. The Tukey test further revealed a significant increase between t2 and t4, (p = .003) suggesting a recession of the rated tinnitus loudness to the baseline value, 6 months after the training.

2.2.3.2 EEG results

Main outcome Training effects of alpha/delta ratio over the four EEG electrodes used for the neurofeedback are summarized in Figure 6. Repeated-measures mixed model ANOVA suggested a significant effect of the factor *time* for the EEG with the instruction to focus on the tinnitus percept (EEG-WT), $\chi^2(2) = 7.77$, p = .021. Alpha/delta ratio of the resting-state measurement without instruction (EEG-NT) did not vary significantly over time, $\chi^2(2) = 3.54$, p = .17.

For EEG-WT, the alpha/delta ratio showed a significant increase between t1 (M

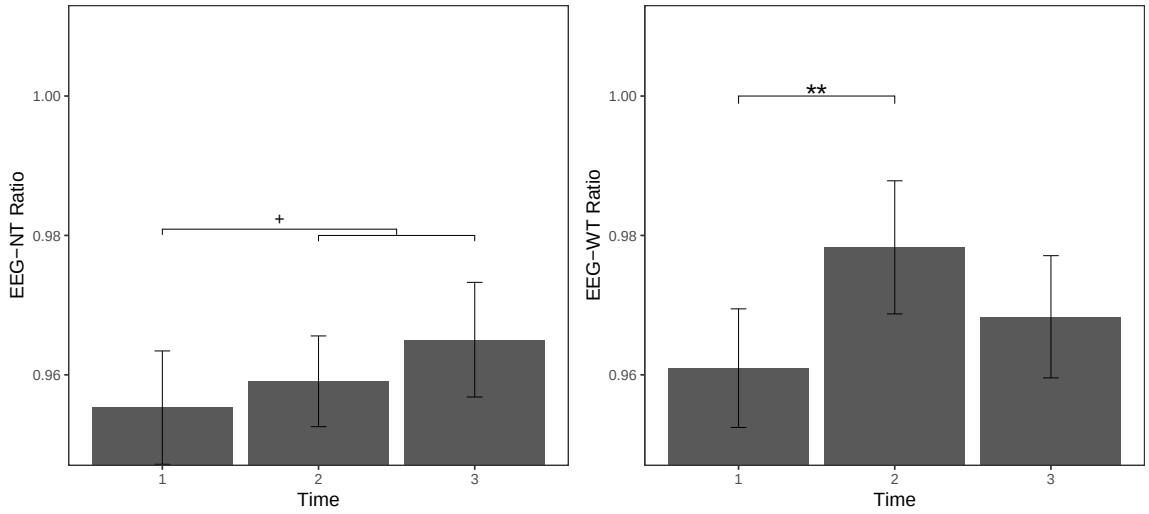

Figure 6: Barplots showing alpha/delta power ratio over the four training-electrodes in measurements before (t1), 1 week after (t2), and 3 months after (t3) neurofeedback training. Error bars represent ±1 standard error for within-subjects designs according to Morey (2008). Alpha/delta ratio of EEG-NT shows an increase between t1 and the two follow-up time-points which was significant on trend-level. Ratio of EEG-WT increased significantly over the course of the training, between t1 and t2, followed by a non-significant decrease to t3.

= 0.961, $SD = 0.0422$) and t2 ($M = 0.9783$, $SD = 0.0443$), $t(46) = 2.83$, $p = .007$ (one-tailed). This increase was followed by a slight decrease measured 3 months after the training, and the difference between t1 and t3 ($M = 0.9683$, $SD = 0.0412$) was thus not substantial enough to yield a significant result, $t(46) = 1.21$, $p = .234$ (one-tailed). This decrease, however, was non-significant as Tukey tests, besides t1-t2, did not show any meaningful differences between time-points. Effect sizes for comparisons were $r = 0.39$ for t1-t2, and $r = 0.17$ for t1-t3.

The contrast analysis for EEG-NT did not reveal any significant results but the comparison between t1 ($M = 0.9553$, $SD = 0.0436$) and the other two time-points combined ($M = 0.9621$, $SD = 0.0361$), suggested a statistical trend in the trained direction, $t(46) = 1.49$, $p = .072$ (one-tailed).

When the individual alpha band as the reward-frequency and the 3-4 Hz fixed delta band as the inhibit-frequency of the neurofeedback training were compared separately, none of the repeated-measures ANOVAs suggested a significant time effect. Nonetheless, a significant decrease in the trained delta band of EEG-WT over the course of the training between t1 ($M = 51.87$, $SD = 1.86$) and t2 ($M = 51.18$, $SD = 1.92$), was found, $t(46) = -2.42$, $p = .02$ (one-tailed).

Control comparisons To control for band specificity of the neurofeedback training, separate analyses were performed for the other (non-trained) frequency bands: theta, beta1, beta2, beta3, and gamma. In addition, the standard bands delta and alpha were analyzed according to their classical definitions of frequency boarders (see section 2.6.2) instead of the ones used for neurofeedback training in this study (3-4 Hz for delta and the individual range for alpha). The alpha was further sub-divided into a lower and an upper alpha-band. The ANOVAs for the two EEG conditions (EEG-NT and EEG-WT) did not suggest any significant effects of the factor *time* and none of the performed contrasts nor the Tukey post-hoc tests showed significant differences between time-points.

Secondly, topographical specificity of the neurofeedback protocol was investigated. In order to assess whether the effects described in the previous section were restricted to the four electrodes used in the training, time effects of the trained alpha/delta ratio averaged over all 65 electrodes of the EEG system were analyzed. Repeated-measures mixed model ANOVA suggested significant effects of the factor *time* for both EEG conditions (EEG-NT: $\chi^2(2) = 9.67$, $p = .008$; EEG-WT: $\chi^2(2) = 9.6$, $p = .008$). For the measurement without instruction (EEG-NT), contrasts only suggested a significant ratio increase between t1 ($M = 0.9636$, $SD = 0.0433$) and t3 ($M = 0.9786$, $SD = 0.042$), $t(46) = 3.2$, $p = .002$ (one-tailed). The effect size of this finding was $r = 0.43$. In the case of EEG-WT, both contrasts showed significant results and meaningful increases were found between t1 ($M = 0.9703$, $SD = 0.0441$) and t2 ($M = 0.9861$, $SD = 0.0457$), $t(46) = 3.1$, $p = .003$ (one-tailed), as well as between t1 and t3 ($M = 0.9815$, $SD = 0.0443$), $t(46) = 2.2$, $p = .033$ (one-tailed). The effect sizes were $r = 0.42$ for t1-t2 and $r = 0.31$ for t1-t3. Tukey post-hoc tests confirmed these findings and suggested no further significant differences.

2.2.3.3 Correlations

To investigate the relationship between training-induced behavioral and electrophysiological changes, difference scores (t2-t1) in the two domains were calculated and compared. Pearson product-moment correlations are summarized in Table 5, as well as in Figures 7 and 8 in Appendix B. Changes in the alpha/delta ratio correlated with THI differences with $r(22) = 0.12$ for EEG-NT, and with $r(22) = -0.12$ for EEG-WT. None of these correlations reached statistical significance. Also for TQ, the negative Pearson correlation coefficient for EEG-NT did not reach statistical significance, $r(22) = -0.03$, $p = .449$ (one-tailed). On the other hand, difference scores of the alpha/delta ratio of EEG-WT suggested a statistical trend for a negative correlation, $r(22) = -0.34$, $p = .053$ (one-tailed). Notably, when analyzed

separately, a significant negative correlation was found between the changes in the trained alpha frequency band and TQ sum-score differences $r(22)$ = -0.4, p = .026 (one-tailed). No significant relationships were found for the trained frequency bands and changes in tinnitus loudness.

Table 5: Summary of Pearson Correlations between Tinnitus and Trained EEG Frequency Band Difference Scores (t2-t1).

	THI	TQ	Loudness
EEG-NT			
Ratio	0.12	−0.03	0.08
IAF	0.25	−0.12	−0.25
Delta	0.10	−0.10	−0.28
EEG-WT			
Ratio	−0.12	−0.34 $^{+}$	−0.14
IAF	−0.06	−0.40 *	−0.11
Delta	0.09	−0.10	0.06

Note. Pearson product-moment correlation coefficients. $^{*}p < .05$ (one-tailed). $^{+}p < .1$ (one-tailed).

Additionally, Pearson correlations between all the fixed standard bands of the two EEG measurements and tinnitus measures were analyzed over the course of the training and are summarized in Table 6. After correction for multiple comparisons with the method of Benjamini and Hochberg (1995), none of the coefficients showed a significant difference to zero. However, when the uncorrected values are taken into consideration, several interesting relationships regarding changes in the alpha band emerge. The standard alpha band (8.5-12 Hz) of both measurements showed negative correlations with THI sum-scores (EEG-NT: $r(22)$ = -0.48, p = .018; EEG-WT: $r(22)$ = -0.46, p = .023). Furthermore, difference scores of the upper alpha-band (10.5-12 Hz) of EEG-NT were found to be negatively correlated with THI changes, $r(22)$ = -0.57, p = .004, as well as with changes in tinnitus loudness, $r(22)$ = -0.44, p = .033.

2.2.4 Discussion

The neurofeedback protocol used in this clinical study aimed at alpha-up, delta-down training with an individualized alpha reward frequency range determined for each patient. Chronic tinnitus patients who participated in this study benefited greatly from the neurofeedback intervention as tinnitus-related distress measured with two different questionnaires (THI and TQ) decreased over the course of training. Fur-

Table 6: Summary of Pearson Correlations between Tinnitus and Standard EEG Frequency Bands Difference Scores (t2-t1).

	THI	TQ	Loudness
EEG-NT			
Delta	−0.04	0.13	0.12
Theta	−0.25	−0.15	−0.31
L-Alpha	−0.17	−0.31	−0.11
U-Alpha	−0.57 **	−0.37	−0.44 *
Alpha	−0.48 *	−0.14	−0.15
Beta1	0.14	0.20	0.14
Beta2	0.14	0.16	0.10
Beta3	0.00	0.01	0.20
Gamma	0.01	0.21	0.35
EEG-WT			
Delta	0.07	0.04	0.16
Theta	0.01	0.06	−0.05
L-Alpha	0.14	−0.14	−0.24
U-Alpha	−0.19	−0.04	−0.06
Alpha	−0.46 *	−0.12	−0.10
Beta1	0.15	−0.20	0.00
Beta2	0.17	0.18	0.27
Beta3	0.29	0.40	0.30
Gamma	0.09	0.30	0.16

Note. Pearson product-moment correlation coefficient, uncorrected. $^{**}p < .01$. $^{*}p < .05$.

thermore, this decrease in distress was stable and remained on a lower level in both the 3- and 6- month follow-up evaluations. Tinnitus loudness was also found to be significantly decreased due to neurofeedback application. However, unlike tinnitus distress, loudness of the phantom percept increased again after the training was completed and returned to baseline levels in the follow-up period. It is important to note that patients did not report any severe and persisting side effects due to the neurofeedback application.

In line with these results, the two previous neurofeedback studies that worked with comparable protocols also reported improvements for tinnitus-related distress, as TQ values (Dohrmann, Elbert, et al., 2007) as well as THI sum-scores (Crocetti et al., 2011) were significantly diminished after the training and remained stable 6 months after completion of the training period. We were able replicate these findings in our study. However, in both preceding studies, a stable recession for tinnitus loudness was also reported, which was not the case in our investigation since loudness was decreased only temporarily. In what follows, we discuss the most relevant implications that emerge from the comparison of our study with the previous reports. Among others, it will be carefully examined whether data obtained within the scope

of this project can support the hypothesis that our neurofeedback application led to specific training effects, or can be explained as the result of unspecific placebo effects.

2.2.4.1 Analysis of electrophysiological data

One way to approach the placebo issue is to analyze objective (i.e., not voluntarily modifiable) electrophysiological data in order to reveal whether the neurofeedback protocol indeed led to the establishment of the proposed activity patterns in the brains of study participants. Regarding electrophysiological data, both the studies of Dohrmann, Elbert, et al. (2007) and Crocetti et al. (2011) did not include resting-state EEG measurements before and after the whole training period and did not obtain EEG data during the follow-up period. They rather focused their analysis on data obtained during the training phase (before and after each training) where they reported rather unspecific *increasing trends* of alpha/delta ratio over the course of sessions. In contrast to these previous reports, we considered resting-state EEG data obtained before and after the entire neurofeedback training period to be more informative for objective changes in electrophysiological activity patterns as a long-term function of the treatment and thus to be more indicative of neurofeedback learning. Baseline resting-state EEG recording was thus performed in an environment essentially different from the training setting and some time before the actual start of the training period. The comparison with the data obtained after all 15 sessions were completed showed that the trained alpha/delta ratio over the four training electrodes was higher after the training than before, suggesting a successful establishment of the desired frequency patterns. In this context, while a significant increase was found for EEG-WT, data from the EEG-NT condition did not show statistically significant effects but only a trend in the anticipated direction. A possible explanation for this inconsistency might be that, in the EEG-NT measurement, no clear and unambiguous instructions were given besides those to open and close the eyes and reduce muscle movements. During the 8 minutes of measurement, patients were thus free to contemplate whatever came to their minds which might have led to highly heterogeneous emotional reactions and evoked brain processes across measurements. In the other (EEG-WT) condition, however, an explicit instruction was given to the patients, asking them to focus on their tinnitus percept in order to control for unwanted tinnitus-suppressing activity which happens continuously in the brains of chronic tinnitus patients. The enhanced focus on the tinnitus tone might have led to reduced heterogeneity of resting-state situations thereby making them more comparable across the three measurement time-points. Furthermore, also the EEG used for neurofeedback training was registered while a patient's tinnitus was clearly salient thus making the altered EEG rhythms more likely to be reflected

in this resting-state measurement condition. All in all, we believe the significantly and stably increased alpha/delta ratio across the entire training period to provide a valuable indication for the successful establishing of the trained frequency patterns.

2.2.4.2 Control groups

Despite the strong evidence for objective changes in brain activity, the lack of a placebo control group can certainly be seen as a possible limitation of this study. This study did not include a control group mainly due to restrictions of time, infrastructure and funding as well as the various arguments discussed comprehensively in our recently published review (Güntensperger et al., 2017). To name the most important ones, we considered the investment on the part of the tinnitus patients, who received no monetary compensation for study participation, to be clearly out of proportion to justify placebo neurofeedback. Furthermore, we did not want to induce any form of expectation as to whether a subject believed themselves to be in the sham or verum neurofeedback group. Strehl et al. (2017) have suggested that absent success after the first training sessions may automatically evoke misguided ideas on the part of patients to be assigned to the placebo group. This could negatively affect motivation and further treatment success regardless of what group the patients have in fact been allocated to. In a comparison with previously performed studies, the publication of Crocetti et al. (2011) also does not mention the inclusion of a control group. Furthermore, even though Dohrmann, Elbert, et al. (2007) reported the use of an active control group that worked with auditory frequency discrimination training, the legitimization of this group in the comparison to the rather specific neurofeedback setting remains unclear.

However, especially in the field of tinnitus treatment, patients often enter a trial with fairly hopeful expectations as they have already endured a variety of disappointing treatment attempts on their own. This circumstance greatly increases the risk for placebo effects of any intervention and unspecific effects of the training thus have to be considered and discussed (Thibault & Raz, 2017). Therefore, our data analysis attached great importance to minimizing the risk for these unspecific effects of neurofeedback training. In particular, our data analysis closely followed the considerations of Gruzelier (2014c) about specificity of neurofeedback treatments. The author suggested that three distinct forms of specificity have to be fulfilled in order to label a neurofeedback intervention successful: frequency band specificity (effects in the trained frequency bands and only in these bands), topographical specificity (effects over the trained electrodes and only there), and outcome specificity (correlations between changes in brain activity and analyzed behavioral outcomes)

(Gruzelier, 2014c). It will be discussed in the following section whether our data can support these three types of specificity.

2.2.4.3 Training specificity

Regarding *frequency band specificity*, data of this study indeed suggested specific effects in the trained frequency bands. As already discussed above, alpha/delta ratio measured over the four training electrodes increased due to the training and remained on a stable high level in the follow-up period. Furthermore, we did not find any changes in other standard frequency bands which clearly speaks in favor of frequency band specificity for the applied neurofeedback protocol.

Topographical specificity, on the other hand, could not be confirmed with the data of this clinical study. The repeated-measures mixed model analysis of variance did suggest significant ratio-effects over time not only for the four training electrodes but also over all 65 electrodes used for pre, post and follow-up measurements. The neurofeedback protocol used in this study, therefore, did not only affect frequency band power in the vicinity to trained electrodes specifically but led to a rather global effect across the whole brain. This, however, does not come as a big surprise since neurofeedback on the basis of activity measured with a limited number of electrodes on the scalp is generally considered to be rather unspecific, leading to wide-spread effects across the whole brain (Congedo et al., 2004). Unfortunately, neither Dohrmann, Elbert, et al. (2007) nor Crocetti et al. (2011) provided any information about possible activity changes on electrodes besides the trained ones. Furthermore, even Gruzelier (2014c) discusses the general possibility of topographically unspecific effects of surface-based neurofeedback. If the brain is seen as a holistic functional network rather than an aggregation of several strictly localized centers, topographically wide-spread effects of frequency band neurofeedback training should come as no surprise (Gruzelier, 2014c). Also in the context of tinnitus, the view has recently shifted from the localized perspective to a more holistic viewpoint, and several models have been proposed aimed at describing the different (sub-) networks that contribute to the tinnitus percept (e.g., De Ridder et al., 2014; Sedley et al., 2016).

Finally, regarding *outcome specificity*, correlation analyses between difference scores of tinnitus and electrophysiological measures show a rather inconsistent picture. Meaningful negative correlations regarding the trained frequency bands could only be found with the changes in Tinnitus Questionnaire. While a decrease of TQ scores was related to an increase of alpha/delta ratio of EEG-WT on trend-level,

the relation with increments in the rewarded individual alpha band was found to be statistically significant. It thus seems as if the increase in alpha was the driving force behind the improvements of tinnitus-related distress as measured with TQ. However, since also THI-measured distress as well as tinnitus loudness declined over the course of the training, we expected these changes to be related with electrophysiological measures as well, which was not the case. Only when analyzing the standard frequency bands, that were not specifically used for training (e.g., alpha according to the classical definition of 8.5-12 Hz for all participants instead of the individually adjusted bands), a negative relationship was found between THI difference scores and changes in alpha power. Furthermore, standard alpha power of the other EEG condition (EEG-NT) was related to behavioral measures as a negative correlation was found with THI- as well as loudness difference scores. It must be noted again that these effects concerning EEG standard bands did not endure correction for multiple comparisons.

Inconsistencies were also reported in the previous studies with comparable neurofeedback protocols as Dohrmann, Elbert, et al. (2007) found electrophysiological measures to be correlated only with tinnitus loudness but not distress, while Crocetti et al. (2011) reported the exact opposite. In our study, Figures 7 and 8 (see Appendix B) provide a deeper look into the patterns of responder- and non-responder individuals in the study sample. In doing so, obvious neurofeedback responders can be identified as patients who were able to improve their alpha/delta ratio (increase their alpha, decrease their delta) and show reduced tinnitus symptoms (cases in the upper left quadrant for ratio and IAF or in the lower left for delta). On the other side, obvious non-responders are also visible as cases unable to alter electrophysiological activity in the desired direction and not showing any or even positive changes in tinnitus symptoms (points in the lower right quadrant for ratio and IAF or the upper right for delta). However, rather inconsistent cases can be seen too. Several patients indicated having substantially benefited from the training and reported their tinnitus-related symptoms to be significantly lower, yet they did not show any EEG training effects (in the lower left quadrant for ratio and IAF, and in the upper left quadrant for delta). Others proved to be extremely successful in adjusting their brain activity in the intended direction over the course of training but did not report any or hardly any noticeable changes in tinnitus symptoms (in the upper right quadrant for ratio and IAF and in the lower right for delta). Thus, even a superficial visual impression of our data already suggests a considerable amount of variability in the set. While the group in its entirety seems to have benefited from the neurofeedback application on average, a closer inspection of the results suggests a more complex pattern in that we have identified a considerable amount of be-

havioral and/or electrophysiological non-responders. Therefore, a thorough future analysis of responder- and non-responder groups would certainly prove fruitful in order to fathom the characteristics of certain subgroups and pave the way for better-suited neurofeedback protocols for each of them. These advanced analyses of data obtained in the scope of this study will also have to include considerations about the clinical relevance of observed difference scores (e.g., Hall, Mehta, & Argstatter, 2018) and will thus be discussed elsewhere.

2.2.4.4 Conclusion

To summarize, we were able to demonstrate frequency band specificity of our individualized neurofeedback protocol, while the training did not lead to topographically specific but rather global effects. Neurofeedback-induced changes in tinnitus-related symptoms seem to be mainly driven by an increase in alpha rather than a decrease in delta power, and the relationship with the trained bands was strongest for distress measured with the TQ. In the light of the TCD model and the SLIM, this finding suggests that tinnitus distress as well as loudness are more closely related to inhibitory activity in auditory areas reflected in the alpha band. If activity in inhibitory neurons is fostered with neurofeedback training and thus the disturbed excitatory/inhibitory balance readjusted, the tinnitus percept seems to be softened and its distressing component weakened. However, as has been shown, individual reactions to the neurofeedback training are fairly heterogeneous and thus do not speak in favor of outcome specificity on the whole. Even though placebo effects cannot be completely excluded, this study significantly extends current work in the field as most neurofeedback studies do not even take unspecific effects of an intervention into account to start with. All in all, the neurofeedback protocol with individualized reward frequency bands discussed in this article can be seen as a good option in the treatment of chronic tinnitus as distress of tinnitus sufferers was significantly and sustainably reduced, and also for tinnitus loudness a temporary effect was found. More comprehensive analysis of responder- and non-responder data will prove crucial for future studies which will have to continue the work on establishing neurofeedback on an individualized basis and pursue the long-term goal of developing training protocols for the specific needs of each and every tinnitus patient.

2.2.5 Appendix B

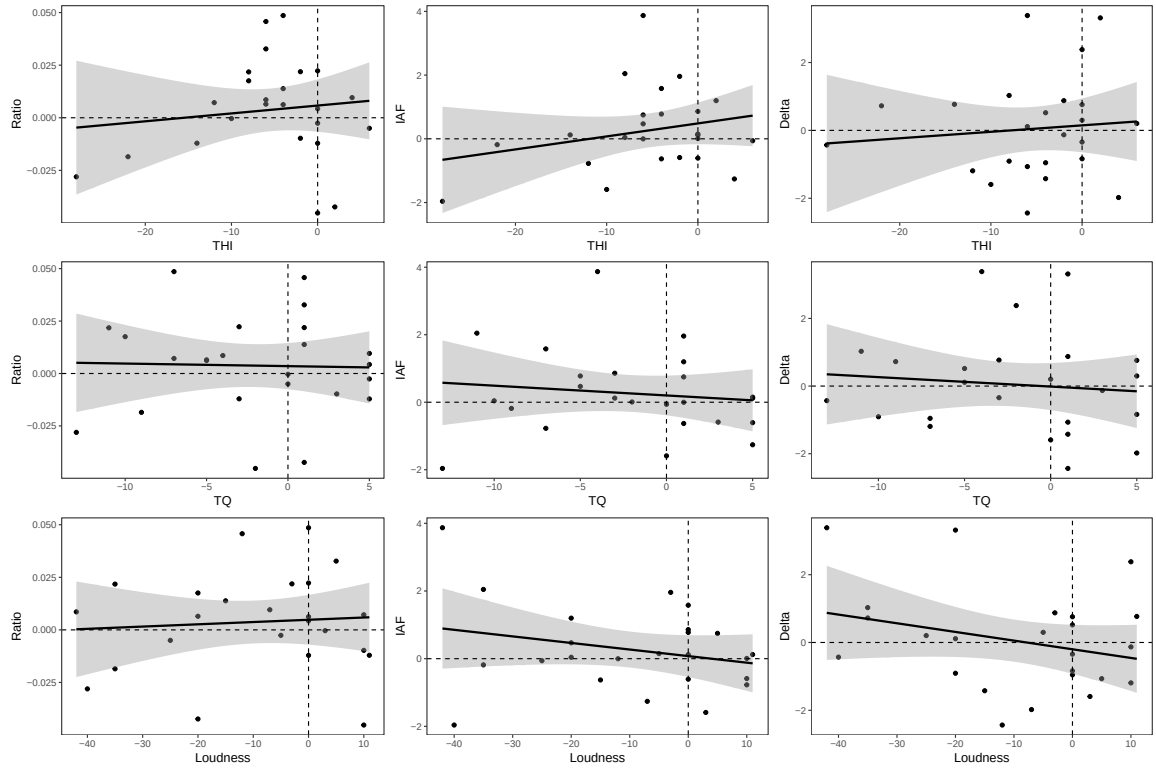

Figure 7: Scatterplots of difference scores (t2-t1) of EEG-NT resting-state data (alpha/delta ratio, rewarded individual alpha frequency range, inhibited delta frequency band) and tinnitus-related symptoms (THI, TQ, tinnitus loudness). The plot shows the fitted regression line with 95% confidence interval. No correlations have found to be statistically significant.

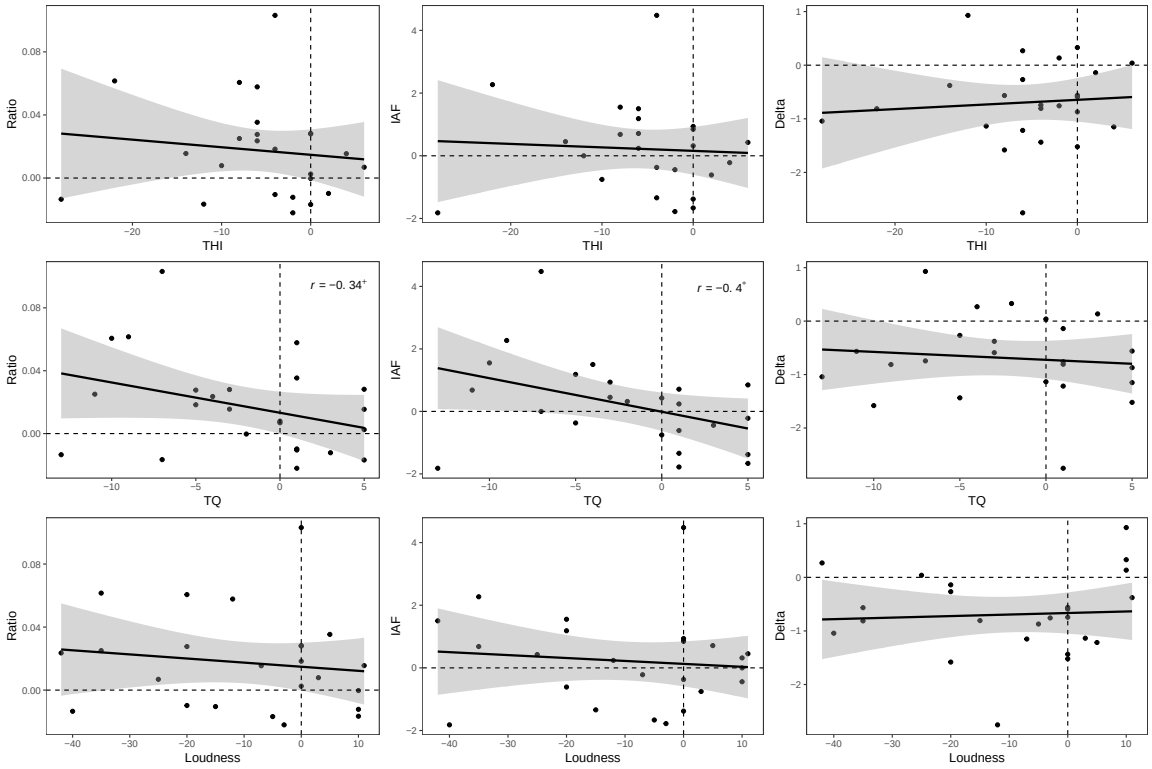

Figure 8: Scatterplots of difference scores (t2-t1) of EEG-WT resting-state data (alpha/delta ratio, rewarded individual alpha frequency range, inhibited delta frequency band) and tinnitus-related symptoms (THI, TQ, tinnitus loudness). The plot shows the fitted regression line with 95% confidence interval. The correlation between IAF and TQ difference scores is statistically significant ($p > .05$). The correlation between ratio and TQ differences reaches trend-level.

2.3 Article III: Evaluation of an sLORETA Neurofeedback Protocol for Treating Chronic Tinnitus.

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A similar version of this manuscript is currently in preparation for submission

Abstract Alpha/delta neurofeedback has been shown to be a potential treatment option for chronic subjective tinnitus. Traditional neurofeedback approaches working with a handful of surface electrodes have been criticized, however, due to their low spatial specificity. The purpose of this study was to evaluate a tomographic neurofeedback protocol that combines activity measured across the whole scalp with sLORETA source estimation. Forty-eight chronic tinnitus patients participated in 15 weekly neurofeedback training sessions and extensive pre and post measurements, as well as follow-up testing (3 and 6 months after the training). Patients were randomly assigned to a tomographic (ToNF) or a traditional electrode-based neurofeedback (NTNF) group. The main outcome measures of this study consisted of tinnitus-related distress measured with the Tinnitus Handicap Inventory (THI) and Tinnitus Questionnaire (TQ), tinnitus loudness, and pre- and post-training resting-state EEG activity in trained frequency bands. For both groups a significant reduction of tinnitus-related distress and tinnitus loudness was found. While distress changes seemed to persist, loudness levels returned to baseline in the follow-

up period. No between-group differences between the 2 neurofeedback applications (ToNF or NTNF) were found, which suggests a similar contribution to symptom improvement. The trained alpha/delta ratio increased significantly over the course of the training and remained stable in the follow-up period. This effect was found for both groups on surface and source levels with no meaningful differences between the 2 groups. This study shows that a tomographic alpha/delta protocol should be considered a valuable addition to tinnitus treatment with neurofeedback. More knowledge about distinct tinnitus subtypes and their manifestation in respective brain activity patterns is necessary in order to develop more individually specific neurofeedback approaches.

Keywords: Tinnitus, neurofeedback, EEG, alpha, delta, tomographic, sLORETA

2.3.1 Introduction

Approximately 5-15% of people in Western societies suffer from chronic subjective tinnitus, which is a condition of a permanent phantom noise, usually described as ringing or hissing in the ears (Henry et al., 2005). For many patients the combination of the penetrating nature of the percept and the lack of treatment options for it leads to severe impairments in quality of life, and sometimes even the development of other health issues and comorbidities such as depression or anxiety (Dobie, 2003; Heller, 2003; Holmes & Padgham, 2008; Langguth et al., 2011).

Electrophysiological recordings with electroencephalography (EEG) or magnetoencephalography (MEG) have recently led to a better understanding of the origin of the chronic phantom sound. It is hypothesized that spontaneous firing of thalamic fibers in a slow-wave mode due to deprived auditory input combined with decreased lateral inhibition processes in the auditory cortex are crucial for tinnitus emergence (De Ridder, Vanneste, Langguth, & Llinás, 2015; Llinás et al., 1999; Weisz, Dohrmann, & Elbert, 2007). In numerous studies with resting state M/EEG, the repeated findings of enhanced delta (0.5-4 Hz) and decreased alpha (8.5-12 Hz) oscillations in tinnitus patients have been considered to be indicative for these processes (Adjamian et al., 2009; Ashton et al., 2007; Kahlbrock & Weisz, 2008; Lorenz et al., 2009; Schlee et al., 2008; Weisz, Dohrmann, & Elbert, 2007; Weisz, Moratti, et al., 2005; Weisz, Müller, et al., 2007).

Several groups have already tried to implement this tinnitus-specific pattern of spontaneous resting-state brain activity into neurofeedback protocols aiming at reversing the abnormalities found in these frequency bands (Crocetti et al., 2011; Dohrmann, Elbert, et al., 2007; Güntensperger, Thüring, Kleinjung, Neff, & Meyer, 2018). Neurofeedback combines operant conditioning and direct feedback of otherwise not directly perceivable brain activity. By rewarding desired and inhibiting undesired changes in neuronal activity patterns, an implicit learning process is triggered that leads to the permanent establishment of targeted patterns after a sufficient number of training sessions. Neurofeedback currently enjoys great popularity in the treatment of a multitude of psychological disorders, such as attention deficit hyperactivity disorder (ADHD) (Arns et al., 2009; Gevensleben et al., 2009; Lévesque et al., 2006; J. F. Lubar et al., 1995; Strehl et al., 2017), depression (e.g., Kelley et al., 2017) and anxiety disorders (e.g., Mennella et al., 2017). Attempts have also been made to use it in the treatment of chronic tinnitus with the aforementioned alpha/delta protocols being the most promising (for a review, see Güntensperger et al., 2017; Kleinjung, Thüring, Güntensperger, Neff, & Meyer, 2017). It has been

reported that this neurofeedback protocol leads to meaningful reductions of tinnitus-related distress and loudness (Crocetti et al., 2011; Dohrmann, Elbert, et al., 2007; Güntensperger et al., 2018). Furthermore, these behavioral changes have been found to be linked to training-induced changes of resting-state brain activity, suggesting specific effects of the protocol.

Despite recent success, traditional neurofeedback protocols using EEG to measure feedback-relevant brain activity have been criticized due to their low spatial specificity. Even though electrodes on the scalp are able to convey electrical brain activity in real time, the exact sources or *neural generators* of the measured signal are usually unknown. In EEG research this issue has commonly been referred to as the inverse problem (Helmholtz, 1853). With neurofeedback protocols in which only a few electrodes on the scalp are used for measuring feedback-relevant aspects of brain activity, it is thus not possible to limit the effects of the training to specific brain areas. Rather, it is highly likely that the effects occur on a more global level and influence multiple brain regions and processes unspecifically (White et al., 2014).

Inverse solution algorithms have been developed recently with the goal of estimating the neural generators of the EEG signal. Since the inverse problem is unsolvable by definition, certain a priori constraints related to physiological properties of EEG signal generation are necessary (Michel et al., 2004). Neuronal sources of recorded EEG on the scalp can thus only be *estimated*, and every solution entails uncertainty depending on the physiological plausibility of the underlying constraints. Frequently used techniques are Low Resolution Electromagnetic Tomography (LORETA) (Pascual-Marqui et al., 1994), its improved version, Standardized Low Resolution Electromagnetic Tomography (sLORETA) (Pascual-Marqui, 2002) and Beamformer algorithms (van Veen et al., 1997).

To increase spatial resolution, *tomographic neurofeedback* (ToNF) protocols have been developed that combine classical single-electrode (NTNF) approaches with EEG source estimation techniques. The researchers Congedo et al. (2004) were the first to publish their work with this newer tomographic method. This group designed their neurofeedback protocol by combining the brain signal measured with 19 active electrodes with an implemented LORETA source estimation. In doing so, six healthy subjects were able to increase their beta/alpha ratio in the training region, defined as the anterior cingulate cortex (ACC). Follow-up studies used beta-training in the ACC with the same algorithm to increase working memory, attention, and self-regulation processes in order to develop treatments against addiction disorders or ADHD (Cannon et al., 2007; Cannon et al., 2006; Cannon, Lubar, Sokhadze, &

Baldwin, 2008). Furthermore, the sLORETA algorithm has been used in studies with ADHD children (Liechti et al., 2012; Maurizio et al., 2014). Also in these studies, ACC was targeted as theta/beta ratio was intended to be altered; however, with only moderate success. Recently, Hartmann et al. (2013) used a self-constructed tomographic neurofeedback method for the treatment of chronic tinnitus. Eight subjects trained an increase of alpha activation while dipole-source space projection was used to estimate the recorded activity of 32 EEG electrodes in two regional dipole-sources situated in the temporal cortex. Tinnitus-related distress was significantly lowered after the training period and a significant increase of alpha activity over the right primary auditory cortex (PAC) was found. The group of Vanneste, Joos, Ost, and De Ridder (2016) has also used tomographic neurofeedback for tinnitus treatment by applying LORETA source estimation. A group of 58 tinnitus patients received alpha-up, beta- and gamma-down neurofeedback over the posterior cingulate cortex (PCC) or the lingual gyrus. A decrease in tinnitus-related distress was reported for the PCC-group, which was attributed to neurofeedback-induced changes in functional and effective connectivity between PCC and different areas of the distress network.

Even though tomographic EEG neurofeedback has thus already been proven to hold great potential, only two studies have as yet attempted to implement it in tinnitus treatment. Therefore, the purpose of this project was to compare a tomographic neurofeedback protocol with an already established traditional neurofeedback option and to evaluate its benefits in the treatment of chronic subjective tinnitus. In this context, an sLORETA algorithm was chosen for source estimation because this technique has repeatedly been shown to be highly precise and can be considered one of the universally accepted and applied methods in EEG research (e.g., Mulert et al., 2004). In our recent work we used alpha/delta neurofeedback with an individually adjusted alpha reward band which led to improvements of tinnitus-related symptoms and EEG alterations in the desired direction (Güntensperger et al., 2018). Feedback-relevant EEG was measured with only four fronto-central electrodes (FC1, FC2, F3, F4) that were chosen according to previous studies (Crocetti et al., 2011; Dohrmann, Elbert, et al., 2007) because they were hypothesized to represent activity of the PAC (Pantev et al., 1995). Even though the trained alpha/delta ratio did in fact increase over the trained surface area, this effect was not specific to the trained electrode sites but was spread over the whole scalp. In this study we also included a second group of tinnitus patients. The training protocol for this group was the same but feedback-relevant activity was measured with 31 (instead of 4) active EEG electrodes and an implemented sLORETA source estimation algorithm aimed at limiting training effects to the PAC. It was hypothesized that ToNF, when

compared with the traditional NTNF application, would lead to at least an equal improvement regarding tinnitus symptoms. Furthermore, it was expected that the EEG-related effects would be more specific over auditory areas for ToNF.

2.3.2 Methods

2.3.2.1 Participants

Participants were recruited at the Department of Otorhinolaryngology (University Hospital Zurich). In order to be eligible for study inclusion, patients had to be diagnosed with chronic subjective tinnitus ($>$ 0.5 years), be between 18 and 75 years old, have adequate knowledge of the German language, suffer from no other psychiatric or neurological disorder, and have no acute suicidal tendency. Furthermore, patients with drug or alcohol addiction, cochlear implants, and current prescriptions for tranquilizers, neuroleptics, or antiepileptics were not considered. According to these criteria, 53 suitable patients with chronic subjective tinnitus were included. Three participants did not finish all 15 neurofeedback sessions (two due to timely restrictions and one because of new medication) and were thus excluded from data analysis. Furthermore, two patients who completed the full study procedure had to be excluded because their depression scores at all four time points suggested clinically relevant depressive symptoms (i.e., BDI sum-scores of more than 18 points). Further, it should be mentioned that one patient unfortunately died due to an unrelated health issue before the last follow-up measurement could be completed. Nevertheless, since the patient finished the full training procedure as well as the first follow-up and did not show any meaningful abnormalities during neurofeedback, the obtained data was included in the analysis.

Table 7 (see Appendix C) shows the demographic and clinical details of the participants included in the final analysis. Participants of the final sample were between 24 and 75 years old with a mean age of 46.83 (SD = 12.8). The sample consisted of 38 males and 10 females. Thirty-five participants described their percept as tonal, three as noise-like, and 10 indicated an undefined type. Most participants (n = 39) perceived tinnitus in both ears, however 16 subjects of this group indicated a left- while 11 specified a right-sided tendency. Four patients indicated a clear left lateralization, three a right lateralized tinnitus, and two experienced it diffusely inside their head. Mean tinnitus loudness was rated as 54.04 (SD = 25.17), mean distress measured with the THI consisted of 32.58 (SD = 17.01) points, and of 26.33 (SD = 14.06) points with the TQ, respectively. These values suggested a “mild tinnitus” according to the THI and a “slight tinnitus” according to the TQ for the overall

group on average.

Participants were randomly assigned to one of two study groups that followed identical study procedures (see section 2.3.2.2) with the sole difference being tomographic (ToNF) or non-tomographic (NTNF) neurofeedback application. The groups were matched according to age, gender, hearing loss, and were of equal size ($n = 24$). Participants were not informed which group they had been assigned to and this study is thus referred to as single-blind randomized controlled trial. The study was approved by the appropriate Ethics Committee (Kantonale Ethikkommission Project KEK-ZH-Nr. 2014-0594) and was online registered at ClinicalTrials.gov (NCT02383147) and kofam.ch (SNCTP000001313).

2.3.2.2 Procedure

This prospective clinical trial consisted of 20 visits in total. In the first appointment, 1-2 weeks before the start of the neurofeedback training phase, patients were extensively informed about the purpose and exact procedure of the study, and signed their informed consent in the presence of a qualified medical professional at the Department of Otorhinolaryngology. In the same visit, participants further underwent the audiometric screening in which their pure tone hearing thresholds at 0.25, 0.5, 1, 2, 4, 6, and 8 kHz as well as other audiometric measurements (speech audiogram and speech-in-noise test) were determined. In the second screening visit, a baseline resting-state EEG measurement was performed and patients were asked to complete questionnaires covering demographics and tinnitus-related symptoms, as well as several other psychological and health-related questions (see details in section 2.3.2.3).

After the two baseline appointments (t1), patients participated in a total of 15 neurofeedback training sessions on a weekly basis. Occasional re-scheduling of individual sessions as well as absences due to holidays or illness were unavoidable and compensated for as best as possible. One week after the completion of the training period, a post-measurement was performed (t2) consisting of the repeated measurement of 16 minutes of resting-state EEG and completion of the questionnaires. The same procedure was repeated around 3 months later when the first follow-up measurement was conducted (t3). In the final follow-up (t4), 6 months after the end of the training period, patients received an online-link by email and were asked for another completion of the set of questionnaires online. Subsequently, they were informed that they had fully completed the clinical study and were provided the opportunity to discuss their individual results with the study team.

2.3.2.3 Behavioral measurements

The set of questionnaires consisted of a variety of forms according to the guidelines of the Tinnitus Research Initiative (TRI) (Landgrebe et al., 2012; Langguth et al., 2007). In particular, an adjusted version of the Tinnitus Sample Case History Questionnaire (TSCHQ) was used to ask about demographics, tinnitus properties (e.g., origin, location, loudness, type), prior treatment attempts, and other tinnitus-related issues. Two questionnaires were used to assess tinnitus distress: the Tinnitus Handicap Inventory (THI) (German version by Kleinjung, Fischer, et al., 2007) and Tinnitus Questionnaire (TQ) (German version by Goebel & Hiller, 1994). Sum-scores can be calculated for both questionnaires ranging from 0-100 in the former, and 0-84 in the latter case. In addition, the TQ score can be divided into the six sub-scores "emotional distress", "cognitive distress", "intrusiveness", "auditory perceptual difficulties", "sleep disturbances", and "somatic complaints".
Additionally, participants completed German versions of Beck's Depression Inventory (BDI) (Hautzinger et al., 1995), Beck's Anxiety Inventory (BAI) (Prinz & Petermann, 2015), the short form of the WHO Quality of Life scale (WHOQOL-BREF) (Angermeyer et al., 2000), Symptom Check List (SCL-K-9) (Klaghofer & Brähler, 2001), and Short Form Health Questionnaire (SF-36) (Bullinger et al., 1995). Completion of questionnaires took about 45 minutes in total and was done electronically on an iPad during the preparation of the EEG system at t1, t2 and t3, and online at t4.
The main behavioral outcome measures of this study are tinnitus loudness (rated from 1 "very low" to 100 "very high"), sum-score of the THI, and sum- as well as sub-scores of the TQ.

2.3.2.4 EEG recording

BrainAmp DC amplifier system in combination with 64 active channel actiCap electrode caps (Brain Products, Munich, Germany) were used to record resting-state EEG at t1, t2, and t3. The array of silver/silver chloride electrodes corresponded with the 5/10 electrode position system (Oostenveld & Praamstra, 2001). Recording was referenced against the FCz electrode with a ground electrode positioned at AFz position. A sampling rate of 1000 Hz was used; the electrodes were prepared with conductive paste for recording, and impedance was kept below 10 kΩ. Recordings were done in direct current (DC) mode with no online filters applied. Patients were asked to sit upright on a comfortable chair in a sound-proof and electromagnetically shielded room and to avoid excessive movements and muscle contractions in order to minimize artifacts. During recording, subjects were instructed by a pre-recorded voice to open (EO) and close (EC) their eyes in regular intervals. For playback of

these instructions, Presentation software (Neurobehavioral Systems, Inc., 2010) was used, and a fixation cross was presented during eyes-open segments. Resting-state EEG was recorded over a time span of 8 minutes, prior to this, the patients were asked to let their tinnitus come naturally and to try not to suppress it. This was done in order to control for unwanted suppression effects that happen continuously in the brains of tinnitus sufferers (see, Sedley & Cunningham, 2013). According to the recommendations of Working Group 3 of the European tinnitus research network, TINNET (see http://www.tinnet.tinnitusresearch.net/), resting-state activity of eyes-open segments was chosen as the main electrophysiological outcome measure.

2.3.2.5 Neurofeedback training

EEG for neurofeedback training was registered with 31 silver/silver chloride electrodes according to the 10/20 system combined with a NeuroAmp amplifier (BEE Medic GmbH, Singen, Germany). Electrodes at the earlobes served as reference electrodes, and AFz as ground electrode. While for the NTNF group only the activity measured at four fronto-central electrodes (FC1, FC2, F3, and F4) was used for feedback generation, the signal of all 31 electrodes was assessed for the ToNF group and combined with the implemented sLORETA source estimation algorithm. For this group the signal estimated at four sources over the primary auditory cortex (Heschl's gyri) was considered relevant for neurofeedback. It is important to note that, even though only four electrodes were feedback-relevant for participants of the NTNF group, all 31 electrodes were prepared for all participants regardless of group affiliation. For recording the sampling rate was set at 500 Hz, and impedance was kept below 20 kΩ. The EEG signal was processed in real-time using the software Cygnet 2.0.3.34 (EEG Info, Kirchberg, Switzerland), and the feedback was implemented in the computer simulation Inner Tube (Somatic Vision, Encinitas, CA, USA). In this visualization, patients observed a space ship automatically navigating through a narrow tunnel. While increased power in the alpha band led to acceleration of the ship, delta as the defined inhibit-band was linked to autopilot accuracy. It is important to note that automatic filtering was included in the Cygnet software so that any kind of movement artifacts (blinking included) as well as system voltage (45-55 Hz) are automatically detected and excluded from feedback.

In the first neurofeedback training session, an individual alpha peak was determined for each participant by averaging alpha peaks over 30 seconds of resting-state EEG (Klimesch, 1999). Subsequently, the reward frequency was set in the range of ±2 Hz around this peak frequency. In contrast, the frequency range of 3-4 Hz corresponding to the delta band was generally set to evoke negative feedback. Patients were asked to sit comfortably in a chair, avoid excessive muscle movement and

pay close attention to the feedback game. Following the custom of previous studies (Crocetti et al., 2011; Dohrmann, Elbert, et al., 2007), no further instruction was given as to how to influence the feedback or what strategy to use in order to allow for the highest amount of freedom possible. The training itself lasted 15 minutes and was repeated once a week, preferably on the same weekday at the same time.

2.3.2.6 Data analysis

EEG preprocessing Preprocessing of EEG data was done with BrainVision Analyzer 2 (Brain Products, Munich, Germany). Data was first band-pass filtered with Butterworth zero-phase filers between 0.1 Hz and 80 Hz with slopes of 24 dB/octave at the low, and 48 dB/octave at the high cutoffs. In order to eliminate possible line noise, data was further filtered with a band-rejection filter with a central frequency of 50 Hz, a bandwidth of 1 Hz, and a slope of 24 dB/octave. The EEG signal was split into independent components in order to identify regular artifacts (e.g., eye-blinks, pulse artifacts, noise). This was done by applying an independent component analysis (ICA) with a restricted Infomax algorithm implemented in BrainVision Analyzer 2. Bad (i.e., very noisy or dead) channels were temporarily excluded from this step. With the inverse ICA procedure, the resulting components indicative of artifacts were removed from the data. Subsequently, spline-type topographical interpolations were performed for previously excluded channels and channels with remaining noise. A thorough visual inspection was performed in order to remove remaining vertical artifacts (i.e., muscle movements, short drifts or jumps over single or multiple electrodes) from the signal. An average reference over all channels was calculated and applied whereby the implicit reference of data recording (FCz) was re-included into the data and used for subsequent analysis. Finally, data was segmented into eyes-closed and eyes-open conditions and imported to MATLAB Statistics Toolbox Release 2017a (The MathWorks Inc., Natick, Massachusetts, United States), EEGLAB 14.1.1b (Delorme & Makeig, 2004), and the LORETA toolbox (version 20150810).

EEG analysis A hamming window with 2s window length and 1s overlap was first applied on the data of eyes-open segments. Surface-based analysis was performed in EEGLAB where a Fast Fourier Transform (FFT) was computed for each 2s-segment. Values were logarithmized and averaged over all segments for each patient. The resulting values provided power values in decibel (dB) for each electrode of the EEG segments with a frequency resolution of 0.5 Hz. Alpha/delta ratio was calculated by dividing power values in the rewarded (individual) alpha range by those in the inhibited delta range (3-4 Hz). This ratio was then averaged over the four electrodes used for training (FC1, FC2, F3, F4) of the NTNF group.

Analysis on source-level was performed using the LORETA toolbox. Technical details of implemented power analysis and source estimation are provided in Pascual-Marqui (2002). The lead field behind the sLORETA algorithm is described in M. Fuchs, Kastner, Wagner, Hawes, and Ebersole (2002) and the integrated electrode position system in Jurcak, Tsuzuki, and Dan (2007). Standard electrode positions were registered with the integrated tool and the transformation matrix was regularized according to the estimated signal to noise ratio of 100. The analysis of log-transformed sLORETA data in the frequency domain resulted in mean current density values (mA/mm^2) that were exported and averaged over the four voxels used for neurofeedback training of the ToNF group (55/-25/10 and 55/-30/10 for right Heschl, -55/-25/10 and -55/-30/10 for left Heschl).

Statistics Data was analyzed using the software package R (R Core Team, 2017) including packages "ggplot2" (Wickham, 2009), "ggsignif" (Ahlmann-Eltze, 2017), "Hmisc" (Harrell Jr, 2017), "jtools" (Long, 2017), "multcomp" (Hothorn et al., 2008), "nlme" (Pinheiro et al., 2017), and "xtable" (Dahl, 2016). Repeated-measures mixed model analysis of variance (ANOVA) was used to estimate time effects for behavioral (THI sum-score, TQ sum- and sub-scores, tinnitus loudness) and EEG-related data. Additionally, a model with group-by-time interaction was fitted to the data in order to reveal potential differences between the ToNF- and NTNF group. A priori defined contrasts comparing t1 with all other time-points (t2, t3, t4 for behavioral measures; t2, t3 for EEG data) were calculated to gain insight into training success and the stability of changes in the follow-up period. Since contrasts are not independent, Bonferroni correction was applied, and, because they were set a priori, one-tailed p-values are here reported. Effect sizes r for a priori defined contrasts were converted from respective t-values according to Field et al. (2012, p.580-581) and will be reported additionally. Cohen (1988) suggests that $r = 0.1$ may be labelled a small, $r = 0.3$ a medium, and $r = 0.5$ a large effect. In addition, post-hoc Tukey tests were performed comparing each of the four time-points with each other in order to reveal other potential differences between time-points. The alpha threshold was set at $p = .05$ for all statistical tests.

2.3.3 Results

2.3.3.1 Behavioral results

Results concerning changes in tinnitus-related symptoms of both neurofeedback groups (ToNF group: group with tomographic neurofeedback, NTNF group: group with surface-based neurofeedback) are summarized in Figure 9. Analysis was performed for both groups combined. Results for the ToNF group can be found in

Tables 8 and 9 (see Appendix C). Data analysis of the NTNF group has already been discussed elsewhere (Güntensperger et al., 2018).

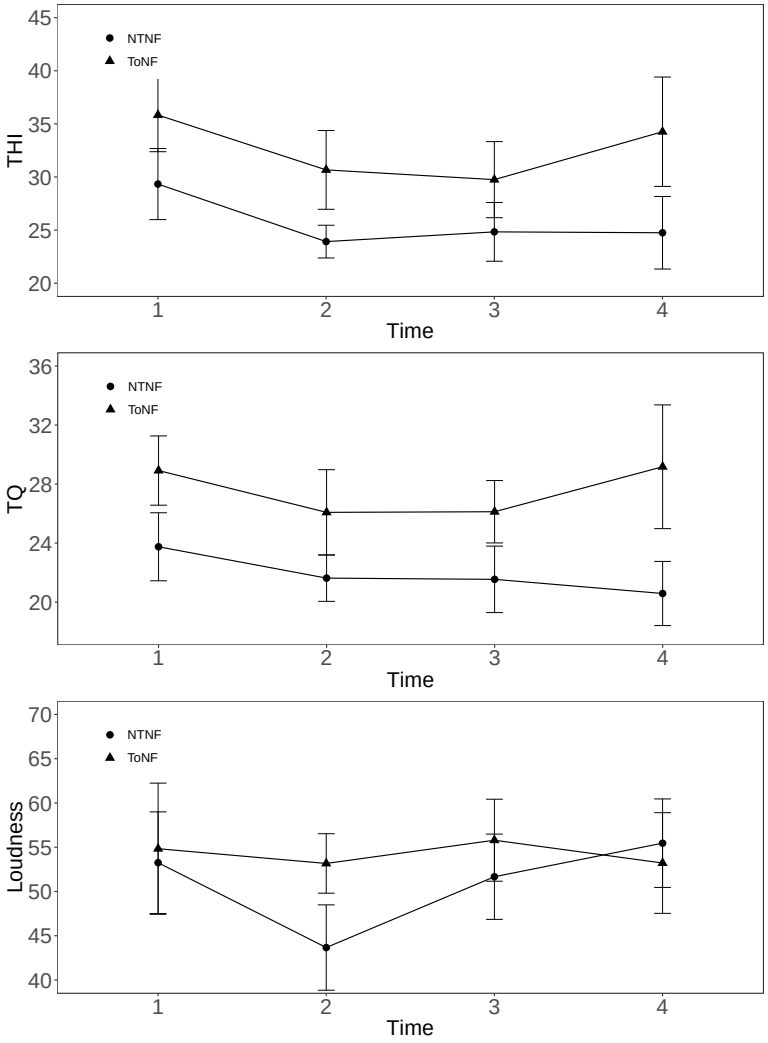

Figure 9: Plots showing tinnitus-related symptoms for the two neurofeedback groups (ToNF group: tomographic neurofeedback, NTNF group: surface-based neurofeedback) before (t1), 1 week after (t2), 3 months after (t3), and 6 months after (t4) training. Error bars represent ±1 standard error for within-subjects designs according to Morey (2008).

THI The results of the repeated-measures mixed model ANOVA suggested a significant effect of the factor *time* on tinnitus distress measured with THI, $\chi^2(3) = 13.11$, $p = .004$. The group-by-time interaction model showed no improved fit on the data $\chi^2(4) = 3.65$, $p = .455$.

A priori defined contrasts showed a significant decrease between t1 ($M = 32.58$, $SD = 17.01$) and t2 ($M = 27.29$, $SD = 15.44$), $t(140) = -3.17$, $p = .003$ (one-tailed). This decrease was persistent up to 3 months after completion of training

since a significant difference between t1 and t3 (M = 27.29, SD = 18.34), $t(140)$ = -3.17, p = .003 (one-tailed) was found. However, the difference between t1 and t4, 6 months after the training (M = 29.4, SD = 20.77), $t(140)$ = -2.01, p = .07 (one-tailed) was not significant. Post-hoc Tukey tests corroborated the significant results and revealed no further significant differences. Effect sizes were $r = 0.26$ for t1-t2, $r = 0.26$ for t1-t3, and $r = 0.17$ for t1-t4, and all effects can thus be considered small.

TQ The results of the repeated-measures mixed model ANOVA suggested no significant effect of the factor *time* on tinnitus distress measured with TQ, $\chi^2(3)$ = 5.42, p = .143. The group-by-time interaction model showed no improved fit on the data $\chi^2(4)$ = 5.95, p = .203.

A priori defined contrasts between t1-t2, t1-t3, and t1-t4 suggested no significant changes of TQ sum-scores. Effect sizes were $r = 0.17$ for t1-t2, $r = 0.17$ for t1-t3, and $r = 0.1$ for t1-t4, and all effects can thus be considered small. However, when the baseline values before the neurofeedback (M_{t1} = 26.33, SD_{t1} = 14.06) are compared with the mean of the three time-points after the neurofeedback sessions ($M_{t2,3,4}$ = 24.16, $SD_{t2,3,4}$ = 15.43), a significant decline was found $t(140)$ = -2.12, p = .018 (one-tailed). Post-hoc Tukey tests revealed no further significant differences.
Furthermore, the repeated-measures mixed model ANOVA suggested no significant effects of the factor *time* on any of the TQ sub-scores.

Loudness The results of the repeated-measures mixed model ANOVA suggested a significant effect of the factor *time* on tinnitus loudness, $\chi^2(3)$ = 7.92, p = .048. The group-by-time interaction model showed no improved fit on the data $\chi^2(4)$ = 5.04, p = .283.

A priori defined contrasts showed a significant decrease between t1 (M = 54.04, SD = 25.17) and t2 (M = 48.42, SD = 25.52), $t(140)$ = -2.19, p = .045 (one-tailed). This decrease, however, was not persistent since no significant difference between t1 and t3 (M = 53.73, SD = 25.23), $t(140)$ = -0.12, p = 1.355 (one-tailed) and neither between t1 and t4, 6 months after the training (M = 54.36, SD = 25.02), $t(140)$ = 0.37, p = 1.07 (one-tailed) was found. Effect sizes were $r = 0.18$ for t1-t2, $r = 0.01$ for t1-t3, and $r = 0.03$ for t1-t4. The Tukey test further revealed a significant increase between t2 and t4, (p = .05) suggesting a recession of the rated tinnitus loudness to baseline values 6 months after the training.

2.3.3.2 EEG results

Results concerning changes of EEG data on both surface and source levels of both neurofeedback groups (ToNF group: group with tomographic neurofeedback, NTNF group: group with surface-based neurofeedback) are summarized in Figure 10. Analysis was performed for both groups combined. Results for the ToNF group can be found in Tables 10 and 11 (see Appendix C). Data analysis of the NTNF group has already been discussed elsewhere (Güntensperger et al., 2018).

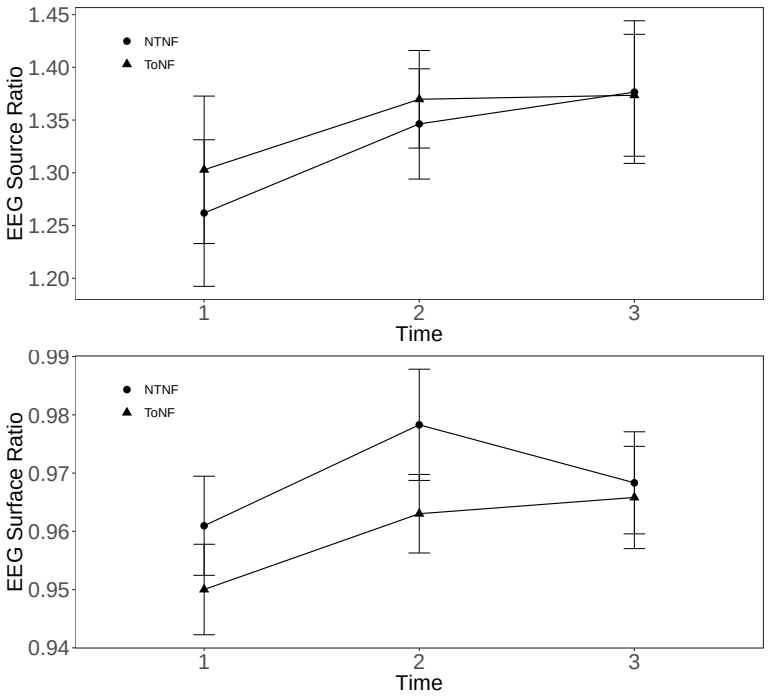

Figure 10: Plots showing alpha/delta ratio for the two neurofeedback groups (ToNF group: tomographic neurofeedback, NTNF group: surface-based neurofeedback) before (t1), 1 week after (t2), and 3 months after (t3) training. EEG data was analyzed on source (over the four voxels used for neurofeedback of the ToNF group) and on surface-level (over the four electrodes used for neurofeedback of the NTNF group). Error bars represent ±1 standard error for within-subjects designs according to Morey (2008).

Source Level The results of the repeated-measures mixed model ANOVA suggested a significant effect of the factor *time* on EEG source data, $\chi^2(2) = 10.88$, $p = .004$. The group-by-time interaction model showed no improved fit on the data $\chi^2(3) = 0.76$, $p = .86$.

A priori defined contrasts showed a significant ratio-increase between t1 ($M = 1.2824$, $SD = 0.1988$) and t2 ($M = 1.358$, $SD = 0.1916$), $t(94) = 2.58$, $p = .012$ (one-tailed). This increase was persistent up to 3 months after completion of training since a significant difference between t1 and t3 ($M = 1.375$, $SD = 0.2319$), $t(94)$

= 3.15, p = .002 (one-tailed) was found. Post-hoc Tukey tests corroborated the significant results and revealed no further significant differences. Effect sizes were r = 0.26 for t1-t2, and r = 0.31 for t1-t3, and all effects can thus be considered small to medium.

Surface Level Training effects of alpha/delta ratio over the four EEG electrodes used for the neurofeedback of the NTNF group showed a significant effect of the factor *time*, $\chi^2(2) = 14.36$, $p < .001$. The group-by-time interaction model showed no improved fit on the data $\chi^2(3) = 3.15$, $p = .369$.

A priori defined contrasts showed a significant ratio-increase between t1 (M = 0.9555, SD = 0.0466) and t2 (M = 0.9707, SD = 0.0499), $t(94) = 3.73$, $p < .001$ (one-tailed). This increase was persistent up to 3 months after completion of training since a significant difference between t1 and t3 (M = 0.9671, SD = 0.051), $t(94)$ = 2.85, p = .005 (one-tailed) was found. Post-hoc Tukey tests corroborated the significant results and revealed no further significant differences. Effect sizes were r = 0.36 for t1-t2, and r = 0.28 for t1-t3, and all effects can thus be considered small to medium.

2.3.4 Discussion

In this project a tomographic alpha/delta neurofeedback protocol (ToNF) based on sLORETA source estimation was used in the treatment of chronic tinnitus for the first time. The two groups of tinnitus patients included in this study followed the training and pre-post test routine in exactly the same way with the single difference being the calculation of their feedback-relevant EEG activity. Both groups aimed at alpha-up, delta-down training with a reward frequency adjusted to their individual alpha peak. However, for the NTNF group the feedback was calculated on the basis of four active electrodes on the scalp as had been done in previous neurofeedback treatment attempts of chronic tinnitus (Crocetti et al., 2011; Dohrmann, Elbert, et al., 2007; Güntensperger et al., 2018). In contrast, for feedback generation of the ToNF group, the signal of 31 EEG electrodes was considered. An implemented sLORETA algorithm ensured that only brain activity with an estimated source in four voxels in the primary auditory cortex was used for feedback. In the following, the results of the data analysis concerning the primary outcome measures of this study are reviewed and critically discussed.

2.3.4.1 Tinnitus-related distress

Tinnitus patients of both groups have benefited from the neurofeedback intervention. Tinnitus-related distress measured with the THI decreased over the course of the training and remained on a stable low level up to 3 months after training completion. Even though 6 months after the training no significant difference was found compared to baseline measures, Tukey post-hoc tests suggested no statistically meaningful increase in the follow-up period. Furthermore, tinnitus-related distress measured with TQ was on a lower level after the training compared to baseline. In this case, contrast analysis of the four time-points did not reveal significant differences but a significant effect was discovered when the mean of the three post-neurofeedback TQ scores was compared to baseline values.

One may wonder whether these differences, statistically significant or not, are also clinically relevant. As simple as this question may sound, there is still no clear consensus in the tinnitus literature about which size of difference can be termed clinically meaningful for patients. Regarding THI, recommended changes range from 6 points (Zeman et al., 2011) up to 20 points (Newman, Sandridge, & Jacobson, 1998). For TQ, the work by Kleinjung, Steffens, et al. (2007) indicated a minimal difference of 5 points to be clinically relevant but Hall et al. (2018) recently suggested a higher cutoff of 12 points. Regardless of the proper criteria, it seems that the tinnitus-related distress of patients in our study did not change in a clinically meaningful way on average . It should be mentioned, however, that neither of these questionnaires were initially developed to account for the measurement of treatment-related change.

In Figure 9 the time courses of tinnitus symptoms are illustrated for the two neurofeedback groups. When visually inspected, members of the ToNF group seem to start out on a higher level compared to the NTNF group. However, the decrease over the course of the neurofeedback training (t1-t2) appears similar for both groups. In addition, the further course of symptoms up to the 3-month follow-up is also comparable. However, visual inspection suggests that members of the ToNF group seem to show a slight recession back to baseline 6 months after the training was terminated. When taking a closer look at individual data trajectories, this was found to be associated with a single patient who showed an extreme increase of tinnitus-related distress between the first and second follow-up measurement (t3-t4). We do not know whether this fact is credited to a dramatic change of the tinnitus percept, an expression of disappointment regarding anticipated treatment expectations, or the simple effects of social desirability since the last follow-up measurement was per-

formed online in an anonymous environment without any examiners present. By all accounts, this case is considered an indisputable outlier which had great influence on the final data analysis of the ToNF group.

Visual inspection of the data thus did not suggest any group specific effects of the neurofeedback protocol. Indeed, the repeated-measures mixed model considering group affiliation of the patients with a group-by-time interaction term did not show an improved fit on data. This suggests that the neurofeedback treatment had roughly the same effect on changes in tinnitus-related distress, regardless of whether the feedback was applied on the basis of only four active electrodes (NTNF) or was acquired with 31 electrodes and source estimation (ToNF). One may wonder why a neurofeedback protocol designed to evoke spatially specific effects on the PAC, the region were occurrence of these maladaptive frequency band alterations have been proposed by TCD and SLIM, does not show superior effects to the unspecific NTNF protocol. Possible reasons for the absence of this between-group difference might be the high interindividual variability of tinnitus manifestation. Recent research in the tinnitus field suggests that tinnitus can hardly be assumed to be the same percept for all sufferers (Landgrebe et al., 2010; Langguth et al., 2013; van den Berge et al., 2017). Rather, it has consistently been shown that many aspects of the tinnitus percept can vary greatly across individuals. Current brain models regarding tinnitus emergence and manifestation take this view into account (e.g., De Ridder et al., 2014; Sedley et al., 2016). Most of these models essentially deflect the focus away from the idea that tinnitus emerges exclusively in auditory areas but rather consider it to be coded in various sub-networks distributed across the whole brain. In this context, a distress network has been proposed that includes structures of the limbic system (e.g., anterior cingulate cortex and amygdala), prefrontal areas (e.g., dorsolateral prefrontal cortex), and also the insula (De Ridder et al., 2014).

Following these considerations, it comes as no surprise that neurofeedback training aimed at causing effects in a distinct part of the brain might not lead to additional benefits regarding tinnitus-related distress. On the contrary, the increased focus on primary auditory cortex areas might be disadvantageous since it does not include relevant areas of the distress network. Unspecific surface-based protocols are able to target multiple areas of the brain simultaneously increasing changes to affect distress-related areas. In the future, tomographic neurofeedback treatments should take into account that areas across the whole brain are involved in tinnitus generation instead of limiting the effects of training to auditory areas exclusively.

2.3.4.2 Tinnitus Loudness

Data analysis revealed that, across the whole study group, neurofeedback led to a significant decrease in tinnitus loudness. However, this decline was followed by an obvious (see Figure 9) and, according to the Tukey post-hoc test, statistically meaningful recession to baseline in the follow-up period. A possible explanation for this issue might be that the number of 15 training sessions was not high enough to affect the loudness of the percept in a sustainable way. However, two studies working with the same protocol (Crocetti et al., 2011; Dohrmann, Elbert, et al., 2007) both reported a stable decrease of tinnitus intensity with 10 and 12 sessions respectively. Another reason for this inconsistency might be the length of the individual neurofeedback session which was 15 minutes in our study and 30 or 20 minutes in the aforementioned studies. Furthermore, patients in our project trained only once per week while the frequency was higher (2-3 times per week) in the previous studies. Therefore, the higher intensity of neurofeedback training might be considered a crucial factor for longer-lasting effects regarding tinnitus loudness.

Also in the case of tinnitus loudness, the repeated-measures mixed model design with group-by-time interaction did not show an improved fit on the data, suggesting no between-group differences. However, as the visual inspection of Figure 9 clearly shows, the decrease in loudness is more pronounced for the NTNF group while the ToNF group shows hardly any change. When the two groups were analyzed separately, no significant effects of the factor *time* on tinnitus loudness were found for the ToNF group, and a contrast analysis suggested no differences between time points (see Tables 8 and 9). Thus, it appears that patients with the unspecific neurofeedback training showed greater loudness improvement. In this case, too, the previous considerations concerning tinnitus sub-networks offers a possible explanation. Regarding the perception of the tinnitus sound, De Ridder, Elgoyhen, et al. (2011) have suggested that activation in the PAC alone is insufficient. For conscious perception to arise, activity in primary sensory areas must be connected to networks composed of regions in the cingulate, parietal and frontal cortex that code importance and salience of percepts. Only when the brain classifies a stimulus as relevant and important, will it be consciously perceived (De Ridder, Elgoyhen, et al., 2011). Since the recruitment of additional brain circuits is necessary for initial perception, also the intensity of a percept (in this case tinnitus loudness) is dependent on this co-activation. Therefore, focusing neurofeedback specifically on auditory areas excludes these networks, a fact which might explain the weaker influence of ToNF on tinnitus loudness.

2.3.4.3 Electrophysiological parameters

An analysis of EEG related parameters was performed in order to have proof of concept that the neurofeedback intervention presented here indeed lead to the proposed effects on brain activity of participants. Source data over the four voxels used for ToNF and alpha/delta ratio over the four active electrodes of the NTNF group suggested that learning of the proposed EEG rhythm occurred in both groups. Repeated-measures mixed model ANOVA revealed a significant effect of the factor *time* and, furthermore, significant ratio increases between pre and post measurements. In addition, these effects could be confirmed 3 months after completion of the training period, suggesting a persistent change in resting-state brain activity.

When a group-by-time interaction term was included in the multilevel model, the fit was not improved. This suggests that, also in the case of electrophysiological changes, no differences between the ToNF and NTNF groups were found. This might come as a surprise as surface-related changes were expected to be more distinct for the NTNF group and changes on source level to be predominant in the ToNF group. However, in the end, both neurofeedback protocols were directed at altering activity over the auditory areas. The four fronto-central electrodes (FC1, FC2, F3, F4) of the NTNF group were chosen because of their high probability to detect activity in perisylvian brain regions according to Pantev et al. (1995) (as cited in Dohrmann, Elbert, et al., 2007). It is therefore valid to assume that the four electrodes also detect activity changes that happened in the PAC of patients in the ToNF group. In addition, global activity changes of the NTNF group also could be manifested in the four voxels on source level which the four training electrodes are believed to represent. This might serve as an explanation as to why the electrophysiological parameters changed equally on surface and source levels for participants of both neurofeedback groups.

2.3.4.4 Conclusion

Alpha/delta neurofeedback seems to be a valid treatment for chronic tinnitus. Surface-based as well as tomographic neurofeedback led to sustainable effects on tinnitus-related distress. In order to alter the intensity of the percept in a sustainable way, a higher frequency (2-3 sessions per week) and longer training sessions (at least 20 minutes) are recommended. Both neurofeedback applications were able to effectively change alpha/delta ratio on both source and surface levels. More research about tinnitus subtypes and their manifestations in the brain is necessary in order to develop more specific tomographic protocols adapted to the individual needs of

each patient.

2.3.5 Appendix C

Table 7: Demographics, Health and Tinnitus Characteristics of Study Sample

	Mean	*SD*[a]	Median	Min	Max
Age					
NTNF	46.29	12.22	44	24	71
ToNF	47.38	13.61	50.5	25	75
Mean Hearing Loss (dB)					
NTNF	7.54	8.25	4.4	0	22.8
ToNF	7.32	8.8	4.05	0	34.4
Tinnitus Duration (months)					
NTNF	78.92	74.63	40	18	312
ToNF	148.04	159.36	114	8	720
Age of Onset					
NTNF	39.75	14.66	39	14	67
ToNF	35.17	13.65	36	7	55
Tinnitus Loudness (0-100)					
NTNF	53.25	19.57	50	20	95
ToNF	54.83	30.16	57.5	8	100
Tinnitus Distress (THI)					
NTNF	29.33	14.7	27	4	56
ToNF	35.83	18.79	31	14	84
Tinnitus Distress (TQ)					
NTNF	23.75	11.63	23	6	45
ToNF	28.92	15.97	31	7	74
BDI sum-score[b]					
NTNF	6.29	4.34	7	0	13
ToNF	5.38	4.17	4	0	15
BAI sum-score[b]					
NTNF	7.12	5.77	6.5	0	21
ToNF	5.25	3.35	4	1	14

Note. [a] *SD*=Standard Deviation. [b] Sum-scales (0-84) measuring severity of depressive/anxiety symptoms.

Table 8: Primary Behavioral Outcome Variables of the ToNF group

	T1	T2	T3	T4
THI	35.83 (18.79)	30.67 (17.37)	29.75 (22.78)	34.26 (23.87)
TQ	28.92 (15.97)	26.08 (15.98)	26.12 (18.10)	29.17 (19.91)
Loudness	54.83 (30.16)	53.17 (27.95)	55.79 (28.43)	53.22 (31.53)

Note. Values are mean (*SD*). T1= baseline. T2=after neurofeedback. T3=3-month follow-up. T4=6-month follow-up. THI=Tinnitus Handicap Inventory. TQ=Tinnitus Questionnaire.

Table 9: Results of the Repeated-Measures Mixed Model ANOVA and a-priori defined Contrasts for Behavioral Data of the ToNF group

	χ^2	t	df	p
THI				
ANOVA	6.32		3	0.097
t1-t2		-1.90	68	0.093
t1-t3		-2.23	68	0.043
t1-t4		-0.75	68	0.681
TQ				
ANOVA	4.37		3	0.224
t1-t2		-1.40	68	0.248
t1-t3		-1.38	68	0.257
t1-t4		0.16	68	1.304
Loudness				
ANOVA	0.53		3	0.912
t1-t2		-0.45	68	0.984
t1-t3		0.26	68	1.197
t1-t4		-0.10	68	1.377

Note. *P*-values of contrast analysis are Bonferroni corrected and one-tailed. T1= baseline. T2=after neurofeedback. T3=3-month follow-up. T4=6-month follow-up. THI=Tinnitus Handicap Inventory. TQ=Tinnitus Questionnaire.

Table 10: Primary EEG Outcome Variables of the ToNF group

	T1	T2	T3
EEG Source Ratio	1.3029 (0.1825)	1.3697 (0.1580)	1.3735 (0.1928)
EEG Surface Ratio	0.9500 (0.0510)	0.9630 (0.0547)	0.9658 (0.0601)

Note. Values are mean (*SD*). T1= baseline. T2=after neurofeedback. T3=3-month follow-up.

Table 11: Results of the Repeated-Measures Mixed Model ANOVA and a-priori defined Contrasts for EEG Data of the ToNF group

	χ^2	t	df	p
EEG Source Ratio				
ANOVA	3.92		2	0.141
t1-t2		1.66	46	0.103
t1-t3		1.76	46	0.085
EEG Surface Ratio				
ANOVA	9.43		2	0.009
t1-t2		2.44	46	0.019
t1-t3		2.96	46	0.005

Note. *P*-values of contrast analysis are Bonferroni corrected and one-tailed. T1= baseline. T2=after neurofeedback. T3=3-month follow-up.

Chapter 3

Discussion

The purpose of this thesis was to investigate the feasibility of neurofeedback (NFB) as a treatment option for chronic tinnitus. In this final chapter, first, a summary about key findings of the empirical research will be provided. Afterwards, results will be discussed regarding their theoretical, methodological, and practical implications. In this context, also future perspectives and currently ongoing research efforts will be presented.

3.1 Summary

The major aim of the first article (see chapter 2.1) was to critically review the effectiveness of neurofeedback treatments for chronic tinnitus. Furthermore, the article comprised a comprehensive summary of electrophysiological tinnitus studies (see Table 2). The goal was to identify possible neuronal correlates of chronic tinnitus or its subtypes. The reviewed studies considered a wide range of chronic tinnitus features (e.g., loudness, distress, pitch, location, age of onset, awareness, or comorbid symptoms) and generally reported alterations of specific frequency bands in related brain areas or networks. Apart from consistent findings for tinnitus distress, which has repeatedly been shown to be represented in limbic and prefrontal structures (e.g., Meyer et al., 2014; Vanneste & De Ridder, 2013), results of these reports were found to be rather diverse and to lack replication. These inconsistencies were discussed in the light of urgently needed guidelines for tinnitus studies (Fuller et al., 2017; Hall, 2017; Hall et al., 2016) and of the efforts currently being made to collect comparable data on tinnitus in a large database (see www.tinnitus-database.de). It was concluded that tinnitus research at this point has not yet been able to identify specific biomarkers for distinct tinnitus subtypes, which greatly limits possibilities for the development of specific neurofeedback protocols.

Eight neurofeedback intervention studies have been identified in the scope of this literature review (see Table 1). Out of these, three publications (Gosepath et al., 2001; Schenk et al., 2005; Weiler et al., 2002) have used unspecific alpha-enhancing training protocols. This technique was not based on previous findings on tinnitus-specific brain activity but rather aimed at inducing a general state of relaxation for tinnitus patients and decreasing their stress level. Focusing more on electrophysiological research findings in the context of the TCD and SLIM model (e.g., Ashton et al., 2007; Lorenz et al., 2009; Weisz, Moratti, et al., 2005), another group developed an alpha/delta NFB protocol. This method has been shown to be a promising approach because tinnitus symptoms were found to be reduced significantly (Dohrmann, Elbert, et al., 2007; Dohrmann, Weisz, et al., 2007; Hartmann et al., 2013). Furthermore, the effectiveness of alpha-up/delta-down training has been successfully replicated by an independent research group (Crocetti et al., 2011). However, the low spatial precision of this and other traditional NFB approaches have been criticized in Article I. Feedback-relevant EEG activity of these approaches has generally been measured with only a few active electrodes on the scalp. This circumstance and the so-called *inverse problem* of EEG research make it impossible to determine the neuronal sources of the signal recorded by these electrodes. Therefore, the feedback-relevant EEG signal always represents a mixture of numerous neuronal generators, and effects of the neurofeedback training can not be limited on distinct regions on the cortex. In the case of tinnitus, TCD and SLIM proposed tinnitus-specific frequency band abnormalities to occur in primary auditory cortex areas. Therefore, it was concluded that combinations between EEG source estimation algorithms and neurofeedback protocols (*tomographic neurofeedback*), which are able to increase spatial specificity of the training, might provide a fruitful addition to tinnitus-related NFB therapy in the future.

Based on these findings and considerations, a large clinical study was conducted in the scope of this dissertation project. Alpha/delta neurofeedback has been chosen as NFB protocol and two groups of tinnitus patients were included. Traditional surface-based (NTNF) and a newer tomographic (ToNF) method of feedback generation have been used. Data collection was carefully organized according to recently developed guidelines for electrophysiological and intervention studies (e.g., Landgrebe et al., 2012). Articles 2 and 3 (see chapter 2.2 and 2.3) summarized the most important findings of this clinical NFB training study.

Data of the non-tomographic neurofeedback (NTNF) group has been analyzed separately to provide information about a possible replication of the previous treatment attempts (Crocetti et al., 2011; Dohrmann, Elbert, et al., 2007; Dohrmann,

Weisz, et al., 2007). Neurofeedback application of this group was nearly identical to these former studies with the sole difference being that the rewarding alpha-band was individually tailored according to the alpha peak frequency. Tinnitus distress (measured with the two established questionnaires, THI and TQ) was found to be significantly decreased after the neurofeedback training period and the level of distress was maintained at follow-up 6 months later. Also tinnitus loudness was reduced directly after the intervention but returned back to baseline in the follow-up phase. Furthermore, Article II (see chapter 2.2) focused on the analysis of electrophysiological data, and resting-state EEG data was compared before and after the training as well as in a 3-month follow-up. Results of this analysis suggested that specific effects of the neurofeedback application led to increasing of the trained alpha/delta ratio over the course of the training period and to the maintenance on a stable higher level in the follow-up measurement. In addition, a variety of correlational analyses and control comparisons were performed to control for unspecific effects of the neurofeedback protocol. Results of these analyses were discussed according to considerations about neurofeedback specificity made by Gruzelier (2014c). It was found that *frequency band specificity* was given since the NFB intervention led to changes in trained frequency bands and only in these bands. However, this study did not confirm *topographical specificity* as the induced changes in oscillation patterns were not limited to the four training electrodes but were found across the whole scalp. Finally, some results of the correlational analyses between electrophysiological and behavioral changes suggested *outcome specificity* but the data was found to be very heterogeneous, with high levels of interindividual differences.

While Article II focused on the replication of previous results and on methodologically sound analysis of EEG data, the main focus of Article III (see chapter 2.3) was put on the comparison between tomographic and non-tomographic feedback application. Results of this comparison suggested no additional benefit of the advanced tomographic training approach (ToNF) regarding tinnitus symptoms and spatial precision. In general, data tentatively indicated even better results for the traditional NTNF group, however, these differences were not statistically significant. This study thus confirmed the initial consideration that more specific biomarkers for distinct tinnitus subtypes are urgently needed in order to develop more specific neurofeedback protocols.

In the following section of this thesis, the major findings of this dissertation project will be discussed with regards to their implications. In doing so, it will be distinguished between theoretical, methodological, and practical implications.

3.2 Implications and Future Perspectives

3.2.1 Theoretical Implications

The reported findings suggested promising effects of alpha/delta neurofeedback on the reduction of tinnitus-related symptoms. In part, this confirms current theoretical models for tinnitus emergence, in particular TCD (Llinás et al., 1999; Llinás et al., 2005) and SLIM (Weisz, Dohrmann, & Elbert, 2007). The fact that trained normalization of tinnitus-specific oscillation patterns proposed by these two models (lower alpha, higher delta) was found to be related to changes in tinnitus symptoms speaks in favor of the proposed processes relevant to tinnitus emergence. However, the results of the empirical studies have also shown that the relationship between electrophysiological and behavioral changes was far from being consistent. A considerable amount of interindividual differences was found in the obtained data, and many subjects reported no changes in tinnitus symptoms despite having successfully altered their EEG activity in the desired direction (see Figures 7 and 8).

Therefore, the reported findings underline the importance of identifying specific biomarkers for chronic tinnitus and (in general) for psychiatric disorders. The seminal work that led to the proposition of the TCD and SLIM model has typically compared resting-state brain activity of tinnitus patients with healthy controls (for a review, see Schlee et al., 2008). Therefore, these comparatively early studies of electrophysiolocial tinnitus research did not take into account the heterogeneous nature of chronic tinnitus. In particular, the percept of tinnitus has been found to be highly individual in terms of subjective manifestation (e.g., intensity, pitch, location) as well as in terms of distress and comorbid symptoms (Landgrebe et al., 2010; Langguth et al., 2013; van den Berge et al., 2017). In a general review on biomarkers, Kapur, Phillips, and Insel (2012) thus suggested to refrain from comparisons between patient- and healthy control groups. Instead, the authors argued that the field should focus more on the exploration of interindividual differences within patient groups to identify biologically homogeneous subtypes for which more specific models and, consequently also treatments, can be developed. The empirical findings of this thesis support this claim, and provide evidence against the aforementioned general tinnitus models and in favour of theories that explain tinnitus as a multifaceted phenomenon such as *global workspace models* (e.g., De Ridder et al., 2014).

A second theoretical implication from this thesis is related to the specificity of neurofeedback effects. In intervention research, effectiveness of a given treatment is

generally verified by showing that its specific effects outweigh its unspecific ones. Examples for unspecific effects are symptom improvement due to a priori expectations (e.g., about the effectiveness of the treatment), the treatment condition in general (e.g., a relaxing setting in which the treatment is applied), and interactions with the practitioner (e.g., the simple meeting with a medical expert) (Thibault & Raz, 2017). This fact that behavioral changes after a certain treatment are not always exclusively caused by the intervention itself has been termed *placebo effect*, which made randomized placebo-controlled trial designs the gold-standard in medicine (Locher, Hasler, & Gaab, 2016). In the context of research with neurofeedback, this issue has often been ignored in previous studies as only behavioral effects have been reported and studies were performed without control groups (Rogala et al., 2016). This made it impossible to distinguish whether specific or unspecific effects were responsible for behavioral changes. However, as the following example shows, an increasing number of scholars insists that placebo effects must also be considered in NFB research. In the last year, many scholars had a heated discourse about exactly this topic in the well-known neurological journal *Brain* (see https://academic.oup.com/brain). This debate was started by an article published by Schabus et al. (2017) who investigated effectiveness of neurofeedback for the treatment of primary insomnia in a double-blind placebo-controlled intervention study. Results of this trial suggested no significant benefits of SMR- over sham neurofeedback on sleep quality. What is more, while objective parameters of sleep quality (e.g., spectral EEG measures) were found to be unaltered by both interventions, subjective measures (e.g., questionnaires about sleepiness and mood) were found to be increased by sham training. In a scientific commentary, Robert Thibault applauded the publication of this article in this high-ranked scientific journal. Furthermore, he and his group were not afraid of general criticism about this neuromodulation technique, calling it a "super-neuroplacebo" without any proven (specific) effects (Thibault et al., 2017b). Supporters of neurofeedback soon replied to these provocative accusations and thus began the dispute (Fovet et al., 2017; Schabus, 2017, 2018; Thibault, Lifshitz, & Raz, 2017a; Witte, Kober, & Wood, 2018).

This dissertation project contributes to this debate and the acquired results speak in favor for specific effects of this treatment. However, one aspct that limits the validity of conclusions about the specificity of behavioral training effects was the lack of a placebo- or any other form of control group. We refrained from using a control group because of ethical reasons and limited resources. Nevertheless, the study was designed to hold risks for unspecific effects to a minimum. For instance, electrophysiological data was measured in resting-state settings at multiple time points (before, immediately after, and 3 months after the NFB training period).

Furthermore, data analysis was planed according to the considerations of Gruzelier (2014c) about specificity of neurofeedback. The author suggested to analyze the data according to *frequency band specificity* (i.e., are EEG effects found in the trained frequency bands and only in these bands?), *topographical specificity* (i.e., are EEG effects found over the trained electrodes and only there?), and *outcome specificity* (i.e., are changes in brain activity and analyzed behavioral outcomes correlated?). Findings of this study revealed significant changes in the trained bands (i.e., alpha and delta) and no other bands. This confirms frequency band specificity and provides a strong argument against placebo effects. Compared to questionnaires measuring behavioral changes, electrophysiological parameters can be considered an objective measure making them less prone to unspecific effects. For instance, patients had no specific expectations regarding brain-related changes, and were thus unable to intentionally modify the outcome of EEG recordings. As mentioned in section 3.1, data of this study did not (or only partially) confirm topographical and outcome specificity. However, the fact that training-induced electrophysiological changes were not related to behavioral ones, is an issue rather questioning theories on tinnitus emergence (see section 3.1) and does not allow to draw conclusions about (un-)specific effects of the NFB protocol. Furthermore, data not revealing topographically specific effects seems to be related to methodological considerations about the measurement of feedback-relevant features in brain activity (see section 3.2.2). Therefore, all in all, findings of this study suggest specific effects of the applied intervention.

3.2.2 Methodological Implications

One of the main goals of this research project was the comparison between the effectiveness of a tomographic and a traditionally applied surface-based neurofeedback method. The surface-based approach (NTNF) has been shown to lead to topographically wide-spread electrophysiological effects that could not be reduced to trained electrode sites. Regarding the application of tomographic neurofeedback (ToNF), which includes more electrodes for recording and the source estimation algorithm sLORETA (Pascual-Marqui, 2002) for improving spatial precision of the training, more regional effects over primary auditory cortex areas were expected. As stated in Article III (see chapter 2.3), training with both (tomographic and non-tomographic) procedures led to comparable behavioral effects which confirmed effectiveness of the newer tomographic method for tinnitus treatment. Furthermore, the results of the electrophysiological analyses performed on surface (over the four training electrodes of the NTNF group) and on source level (over the four training voxels of the ToNF group) suggested alpha/delta ratio increases for both groups. On the one hand, this

means that tomographic neurofeedback training successfully induced the intended changes over PAC areas on source level. On the other hand, however, these alterations were not significantly different from the ones found in the NTNF group. Despite these unexpected findings, it would be premature to conclude that the tomographic method failed to achieve improved spatial precision of the training. First, *absence of evidence* should never be confused with *evidence of absence* (Altman & Bland, 1995). Second, both neurofeedback protocols were designed to alter activity in auditory areas, thus it should come as no surprise that also the NTNF group showed effects on source level. Rather, the fact that both groups were able to increase their alpha/delta ratio on source *and* on surface level in comparable ways, speaks in favour of the four fronto-central electrodes (FC1, FC2, F3, F4) being well-chosen to represent auditory cortex activity (Dohrmann, Elbert, et al., 2007).

Further methodological implications concern the fact that this study can be considered the first neurofeedback trial in the context of chronic tinnitus that took into account individual reward frequencies. Instead of using the fixed alpha-band, commonly defined between 8 and 12 Hz, the individual alpha peak frequency has been determined in the first session towards which the reward band was orientated (± 2 Hz). Even though protocols with IAF have already been investigated for the treatment of other disorders (e.g., Escolano et al., 2014; Zoefel, Huster, & Herrmann, 2011) and the use of individually adjusted reward-bands is highly recommended by many scholars (e.g., Alkoby et al., 2017), this was the first study following this individually tailored approach. The results of Article II (see chapter 2.2) suggested that the use of IAF can indeed be seen as a valuable improvement. Thus additionally, this project represents a step towards more individualized neurofeedback protocols to treat tinnitus.

Finally, the wide range of questionnaires and tests used in this comprehensive clinical study has to be emphasized. This was done in order to best capture the substantial heterogeneity of tinnitus and to not miss any potential effects of the training. Many previous publications in tinnitus research have been criticized because of poor or completely absent definitions of outcome measures, which is traced back to the lack of general standards and guidelines and leads to a missing consensus between different studies. By carefully following the suggestions and newest developments of joined research initiatives such as TINNET, this clinical study made a statement in the right direction: Not only was tinnitus-related distress, the primary outcome measure of the study, captured using multiple measures, but also a variety of other psychological and health-related questionnaires have been used. The large amount of collected data has not yet been fully analyzed and will be subject of

future investigations. A possible analysis, for instance, might concern (behavioral and/or electrophysiological) responder and non-responder groups for which specific psychological profiles could be identified (e.g., by means of factor analyses).

3.2.3 Practical Implications

The neurofeedback protocol used in this project has been found to be a promising treatment option for chronic tinnitus. Patients benefited greatly from the training as their tinnitus-related distress has been permanently, loudness of their tinnitus at least temporarily, reduced. Furthermore, none of the patients reported persisting side effects due to application of the training. Therefore, neurofeedback should be considered as a compelling non-invasive option for clinical practice of tinnitus treatment. This is not to say that this intervention technique should be advertised as some general cure for tinnitus but rather as complementary to other existing forms of treatment (see also section 1.1.4) In particular, a combination with psychotherapy might be fruitful as NFB contributes heavily to experiencing self-efficacy. Many participants reported that they perceived a feeling of control over their tinnitus for the first time since its emergence, which raised confidence in being able to actively improve their situation. If these experiences made during neurofeedback training are properly addressed and discussed in psychotherapeutic settings, its beneficial effects might be intensified.

Further practical implications concern placebo effects of neurofeedback. It is important to note that even though the discussion about whether NFB leads to specific or unspecific training benefits matters, of course, greatly for scholars and people interested in the mechanisms behind it (see section 3.2.1). However, the question *why* neurofeedback works does not really seem to matter for patients themselves. Even in the potentially worst case (i.e., if NFB is indeed reduced to some kind of *super-neuroplacebo*), the fact *that* neurofeedback works for many patients should not be underestimated. Instead of ignoring treatments with a high risk for placebo effects, research should rather be concerned with these unspecific effects as well and aim at understanding their mechanisms. In this context, the publications of F. Benedetti and his group should be highlighted who aimed at addressing this topic and conducted investigations on neurobiological mechanisms of placebo effects (Benedetti, 2006; Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005; Price, Finniss, & Benedetti, 2008). In their research, they clearly stated that, even though certain drugs may be absolutely ineffective for a given treatment, they can still have actual effects on brain and body (e.g. in certain neurotransmitter-systems such as dopamine). Therefore, placebo effects are still *effects* and should not be considered

to be simple response biases. Even more fascinating, in this context, are experiments with open placebos (i.e., placebos without deception). In a study by Kaptchuk et al. (2010), pills that were openly declared as placebos have been found to lead to improvements of certain symptoms (in this case: in irritable bowel syndrome). The authors concluded that it is unlikely that deception or concealment are the crucial elements for placebos to work, and other studies have shown that the surrounding psychosocial context inducing top-down expectations are more important in this regard (Benedetti, 2006; Wager & Atlas, 2015).

Due to these considerations, practical implications arise regarding planning and designing future neurofeedback intervention studies. Unspecific effects of neurofeedback should be investigated, rather than excluded, to determine the full potential of this technique, an opinion even shared by its fiercest critics (Thibault & Raz, 2017). Therefore, to allow for investigations of specific and unspecific effects, future NFB experiments should be well designed, following clinical guidelines, and provide in-depth data analysis (such as comparing responder and non-responder groups) (Alkoby et al., 2017; Friedrich et al., 2014).

3.3 Concluding Remarks

To sum up, this thesis confirmed neurofeedback as a promising treatment option for chronic tinnitus. While besides traditional non-tomographic, also tomographic neurofeedback has shown to improve tinnitus symptoms, future research aiming at identifying more specific biomarkers for distinct clinical subtypes of tinnitus is urgently needed to allow for even more individualized protocols. Furthermore, also unspecific effects of the training have to be analyzed and evaluated so that the effectiveness of neurofeedback interventions can be improved in the future. Finally, by combining neurofeedback with other tinnitus interventions (e.g., cognitive behavioral therapy or other neuromodulatory techniques such as acoustic stimulation), new possibilities arise in the search for an effective treatment strategy for chronic tinnitus.

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jor depressive disorder. *NeuroImage: Clinical*, *17*, 691–703. doi:10.1016/j.nicl.2017.12.004

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https://www.imprs-life.mpg.de/en/people/dominik-guntensperger

RESEARCH INTERESTS

Neuroplasticity of Tinnitus

Neuromodulation of Tinnitus: The treatment of chronic tinnitus with neurofeedback

ACADEMIC EMPLOYMENT AND EXPERIENCE

Doctoral Student and Project Management 08.2015 – today
The Treatment of chronic Tinnitus with Neurofeedback
Department of Psychology, University of Zurich
Chair of Neuropsycholgy, Prof. Dr. Martin Meyer

Research Assistant 12.2014 – 08.2015
Neurophysiological correlates of speaker identification
Zurich Center for Linguistic, University of Zurich
Phonetic Laboratory, Prof. Dr. Volker Dellwo

Research Assistant 11.2014 – 02.2015
Does linguistic salience originate in the brain?
Department of Psychology, University of Zurich
HAB LAB, Prof. Dr. Martin Meyer

Technical Assistant 02.2013 – 04.2015
Division of Educational Development, University of Zurich
Academic Program Development, Dr. Thomas Hidber

Research & Technical Assistant 10.2012 – 04.2015
Division of Educational Development, University of Zurich
Center for University Teaching and Learning, Balthasar Eugster

Research Tutor 12.2008 – 03.2009
Motivational reserve capacity as a protective factor for light cognitive impairment and Alzheimer's disease
Department of Psychology, University of Zurich
Psychopathology and Clinical Intervention, Prof. Dr. Dr. A. Maercker

Student Assistant 03. – 05.2008
Human Resource Management, working relationship and mental state
Department of Management, Technology and Economics, ETH Zurich
Chair of Work and Organizational Psychology, Prof. Dr. Gudela Grote
Department of Business Administration University of Zurich
Chair in Human Resource Management, Prof. Dr. Bruno Staffelbach

EDUCATION

University of Zurich 08.2015 – today
PhD-Candidate in Psychology
Chair of Neuropsycholgy
Advisor: Prof. Dr. Martin Meyer
Co-advisor: Prof. Dr. Mortiz Daum, Prof. Dr. Nathan Weisz

International Max Planck Research School (IMPRS) 12.2015 – today
LIFE Fellow
The Life Course: Evolutionary and Ontogenetic Dynamics

University of Zurich 2012 – 2014
Master of Science in Psychology
Minor: Philosophy
Final grade: 5.8
Thesis: *"Tinnitus and sLORETA-Neurofeedback: A pilot study"*

English Language Center (ELC), Boston 03.2012 – 06.2012
Cambridge Certificate in Proficiency of English

University of Zurich 2007 – 2012
Bachelor of Science in Psychology
Minor: Philosophy
Final grade: 5.7
Thesis: *"(Self-) consciousness – Neuropsychological approaches"*

Cantonal School Wettingen 2001 – 2006
Higher School Certificate
Core subject: Philosophy, Psychology & Pedagogics
Complementary subject: History

INTERNATIONAL COLLABORATIONS

Short Term Scientific Mission at University of Trento 08.2015
CIMeC MEG Laboratory
Supervisor: Prof. Dr. Nathan Weisz

THIRD-PARTY FUNDING

Research travel grant of the Department of Psychology for the 6th International Conference on Auditory Cortex in Banff, Canada. (CHF 1'000) — 2017

Research travel grant of the Faculty of Arts and Social Science (PhF) for the LIFE Academy in Ann Arbor, Michigan, USA. (CHF 907) — 2017

Research travel grant of the Faculty of Arts and Social Science (PhF) for the 10th International Tinnitus Research Initiative (TRI) Conference in Nottingham, UK. (GBP 300) — 2016

Travel grant of the EU COST Action TINNET for the STSM *The efficiency of neurofeedback in the treatment of chronic tinnitus* in Trento, Italy. (EURO 1'500) — 2015

COMPETITIVE INTRAMURAL FUNDING

LIFE grant for the project *The Treatment of chronic Tinnitus with Neurofeedback.* (CHF 10'000) — 2016

AWARDS

Poster Award (2nd prize) at the URPP Dynamics of Healthy Aging In-house Conference, Ittingen, Switzerland. — 2017

PUBLICATIONS

Güntensperger, D., Thüring, C., Meyer, M., Neff, P., & Kleinjung, T. (2017). Neurofeedback for Tinnitus Treatment–Review and Current Concepts. Frontiers in aging neuroscience, 9.

Kleinjung, T., Thüring, C., **Güntensperger, D.**, Neff, P., & Meyer, M. (2017). Neurofeedback for the treatment of chronic tinnitus: Review and future perspectives. HNO.

TALKS

Güntensperger, D. (March, 2018). *Treating Chronic Tinnitus with Neurofeedback.* Presentation at the 11th Tinnitus Research Initiative (TRI) Meeting and TINNET conference, Regensburg, Germany.

Güntensperger, D. (May, 2017). *(Tomographisches) Neurofeedback zur Behandlung von chronischem Tinnitus.* Invited presentation at the General Assembly of the Swiss Neurofeedback Organisation, Zurich, Switzerland.

Güntensperger, D. (May, 2017). *Treating Chronic Tinnitus with Tomographic Neurofeedback.* Presentation at the LIFE Spring Academy, Ann Arbor, Michigan, USA.

Meyer, M., Neff, P., & Güntensperger, D. (October, 2016). *Chronischen Tinnitus wirkungsvoll behandeln mit Neurofeedback?* Invited presentation at the Group Meeting of Prof. Dr. Stefan Büchi, Privatklinik Hohenegg, Meilen, Switzerland.

Güntensperger, D., & Neff, P. (September, 2016). *Tinnitusforschung an der Universität Zürich.* Invited presentation at the Fall Convention of the Swiss Tinnitus League, Zürich, Switzerland.

Güntensperger, D., & Neff, P. (March, 2016). *Neuromodulation und Neurofeedback bei Tinnitus: Forschung am Standort Zürich.* Invited presentation at the General Assembly of the Swiss Tinnitus League, Zurich, Switzerland.

Güntensperger, D. (July, 2015). *Neurofeedback: A Possibility To Treat Chronic Tinnitus?* Invited presentation at the Team Meeting of Prof. Dr. Nathan Weisz, CIMeC MEG Laboratory, University of Trento, Italy.

POSTER PRESENTATIONS

Güntensperger, D., Meyer, M., Thüring, C., Neff, P., & Kleinjung, T. (2017). Treating Chronic Tinnitus with Neurofeedback, Poster presented at the URPP Dynamics of Healthy Aging Inhouse Conference, November 2017, Ittingen, Switzerland.

Güntensperger, D., Meyer, M., Thüring, C., Neff, P., & Kleinjung, T. (2017). Treating Chronic Tinnitus with Neurofeedback, Poster and short talk presented at the LIFE Fall Academy, October 2017, Zurich, Switzerland.

Güntensperger, D., Meyer, M., Thüring, C., Neff, P., & Kleinjung, T. (2017). Treating Chronic Tinnitus with Neurofeedback, Poster presented at the 6th International Conference on Auditory Cortex, September 2017, Banff, Canada.

Güntensperger, D., Meyer, M., Thüring, C., Neff, P., Weidt, S., & Kleinjung, T. (2016). Tomographic Neurofeedback Treatment of Chronic Tinnitus, Poster and short talk presented at the LIFE Fall Academy, October 2016, MPI Berlin, Berlin, Germany.

Güntensperger, D., Meyer, M., Thüring, C., Neff, P., Weidt, S., & Kleinjung, T. (2016). *Neurofeedback Treatment for Tinnitus Patients across the Lifespan*, Poster and short talk pre-

sented at the LIFE Spring Academy, May 2016, University of Virginia, Charlottesville, USA.

Güntensperger, D., Meyer, M., Thüring, C., Neff, P., Weidt, S., & Kleinjung, T. (2016). *Treatment of Chronic Tinnitus with Neurofeedback.* Poster presented at the 10th International Tinnitus Research Initiative (TRI) Conference, March 2016, Nottingham, GB.

Güntensperger, D., & Meyer, M. (2015). *Neurofeedback as a Possibility to Treat Chronic Tinnitus in Older Adults and Implications for Healthy Aging. A clinical study with tomographic neurofeedback.* Poster presented at the Site Visit URPP Dynamics of Healthy Aging, September 2015, Zurich, Switzerland.

Güntensperger, D., & Meyer, M. (2015). *Neurofeedback: A Possibility To Treat Chronic Tinnitus? A pilot study with sLORETA-based Neurofeedback.* Poster presented at the LizentiandInnen-, Masterstudierenden und Doktorierenden-Kongress (LiMaDoKo), May 2015, Zurich, Switzerland.

Güntensperger, D., & Meyer, M. (2014). *Tinnitus and sLORETA-Neurofeedback: A pilot study.* Poster presented at the INAPIC Fall Workshop, September 2014, Zurich, Switzerland.

FURTHER RESEARCH- RELATED ACTIVITIES

Member of the Peer Mentoring Group *Advanced EEG Analysis* 06.2015 – 12.2017
Department of Psychology, University of Zurich, Switzerland

Fieldtrip Workshop 12.2015
EU COST Action TINNET
Centre for Cognitive Neuroscience, University of Salzburg, Austria

Training School in Auditory Neuroscience 05.2015
EU COST Action TINNET
Institute of Experimental Medicine, Academy of Science, Prague, Czech Republic

Certificate for Good Clinical Practice (GCP) 12.2014
TRREE Training Program in Research Ethics Evaluation
Faculty of Law, Institute of Health Law, University of Neuchâtel

MRI Safety Course 2014
University Hospital Zurich, Switzerland

TEACHING EXPERIENCE

Teaching Assistant *Practical Course in Experimental Psychology* 2015
Department of Psychology, University of Zurich, Switzerland

STUDENT SUPERVISION

Master Students:	Amela Jakupovic (2016 - 2017)
Bachelor Students:	Alessandra Schöpke (2017), Amelie Zacher (ongoing), Elia Montevecchi (ongoing)
Research Assistants:	Maria Kliesch (2015 - 2017), Christine Stoquet (2015 – 2016), Barbara Lewis (2015 - 2016), Samanta Wurmitzer (2015 - 2016), Madlaina Mugwyler (2015 - 2016), Raphaela Muri (2015 - 2016), Isabella Hillmer (2015 – 2016)
Research Interns:	Alice Ghidossi (2017), Julian Hofmann (2017), Nina Hüsser (2016), Eva Silberschmidt (2016), Marie Von Seeler (2015 – 2016), Maximiliane Ekert (2015), Kristopher Karg (2015)

LANGUAGES

German:	language proficient , C2 (native language)
English:	language proficient , C2 (Cambridge Certificate in Proficiency of English 2012)
French:	good knowledge, both written and spoken, B1
Latin:	basic knowledge, written (complementary exam University of Zurich 2008)
Russian:	basic knowledge

IT SKILLS

MS Office, EvaSys, Citavi, Cygnet (EEG Info), BrainVision Analyzer, R, MATLAB, EEGLab	very good knowledge
SPSS, Latex, LORETA	good knowledge
Presentation, Fieldtrip	basic knowledge